JZKA Protocol (b)

Phase 1/2 Study of LY3499446 Administered to Patients with Advanced Solid Tumors with *KRAS* G12C mutation

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Approval Date: 21-Jan-2020

Title Page

Protocol Title: A Phase 1/2 Study of LY3499446 Administered to Patients with Advanced Solid Tumors with *KRAS* G12C mutation

Protocol Number: J2K-MC-JZKA

Amendment Number: (b)

Compound Number: LY3499446

Study Phase: Phase 1/2

Short Title: A Study of LY3499446 in Patients with Advanced Solid Tumors with *KRAS* G12C mutation

Acronym: JZKA

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 144905

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 21-Jan-2020 GMT

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	07-Oct-2019
Protocol J2K-MC-JZKA	22-Aug-2019

Amendment (b)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to update the Phase 1 portion of the study as a result of observed safety signals in initially enrolled patients, as well as to provide additional safety guidance for investigators.

Section # and Name	Description of Change	Brief Rationale
Throughout	Revision of Phase 1 dose escalation dosing, cohorts, and schedule	Dose escalation design revised for safety
Section 1.3 Schedule of Activities	Visits 4, 11, and 18 added; additional hematology and chemistry visits included on visits 4, 11, and 18 of Cycles 1 and 2.	Visits added to monitor for safety
Section 1.3 Schedule of Activities	Modified baseline and on-treatment visit windows for Phase 1 patients	Visit windows modified for improved alignment with study strategy
Section 1.3 Schedule of Activities; Section 6.1 Study Intervention(s) Administered	Removal of 1-week lead-in for cetuximab	Revised to align with updated study strategy
Section 1.3.1 Sampling Schedule for PK and ECGs for Participants in Phase 1	Time windows added for PK draws; additional PK sampling included for Cycle 1	Time windows added to provide flexibility; sampling added to align with study changes
Section 2.3 Benefit/Risk Assessment	Updated benefit/risk description of LY3499446	Section updated to provide up-to-date safety information
Section 4.3 Justification for Dose	Updated justification of starting LY3499446 dose	Starting dose updated due to observed safety signals

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	New criterion added	Criterion added to align with revised dose escalation strategy
Section 6.5 Concomitant Therapy; Appendix 9	Added CYP2C9 and CYP2C19 language for LY3499446; Appendix added	Cautionary language and appendix added as guidance for investigators
Section 6.6.1 Dose modification of LY3499446	Added guidance table and language for treatment-emergent adverse events suggestive of hemolysis	Additional guidance provided for investigators
Section 6.6.2 Dose Modification of Abemaciclib; Section 6.6.3 Dose Modification of Cetuximab	Addition of dose modification guidance for abemaciclib and cetuximab	Detailed dose modification guidance provided for greater clarity
Throughout	Minor editorial and formatting changes	Minor, therefore not summarized

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1/2 Study of LY3499446 Administered to Patients with Advanced Solid Tumors with *KRAS* G12C mutation

Short Title: A Study of LY3499446 in Patients with Solid Tumors with *KRAS* G12C mutation

Rationale:

More than 30% of all cancer types possess mutations in RAS. *KRAS* mutations account for approximately 85% of *RAS*-associated cancers in humans and have typically been associated with worse overall survival and increased resistance to treatments compared to *KRAS* wild-type tumors (Dinu et al. 2014; Ferrer et al. 2018; Windon et al. 2018). *KRAS* mutations occur in approximately 16% to 40% of non-small cell lung cancer (NSCLC), and G12C mutations represent approximately 40% of total mutations in NSCLC (Fernández-Medarde and Santos 2011). However, due to its lack of deep pockets for binding of small molecule inhibitors, RAS is typically deemed as "undruggable." Various anti-RAS therapeutic strategies have been proven largely ineffective (Ferrer et al. 2018; Román et al. 2018; O'Bryan 2019). Recent studies have been focusing on *KRAS* mutation-specific therapies.

LY3499446 is a potent and orally available small molecule inhibitor of *KRAS* G12C, CCI [redacted] nd has demonstrated significant activity in preclinical models against a wide range of *KRAS* G12C mutant tumors.

Study J2K-MC-JZKA (JZKA) consists of a Phase 1, open-label, dose-escalation study of LY3499446 as monotherapy or in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation followed by a randomized controlled Phase 2 study of LY3499446 administered as monotherapy or in combination with abemaciclib or erlotinib in patients with NSCLC tumors harboring *KRAS* G12C mutations, and of LY3499446 administered as monotherapy or in combination with cetuximab in patients with colorectal cancer (CRC) harboring *KRAS* G12C mutations, and an expansion of LY3499446 monotherapy in patients with *KRAS* G12C mutant solid tumors, other than NSCLC and CRC.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1 Dose Escalation: • To characterize the RP2D for LY3499446 when administered alone or in combination with either abemaciclib, cetuximab, or erlotinib.	• DLTs • Assessment of safety including, but not limited to, TEAEs, SAEs, deaths, and clinical lab abnormalities per CTCAE v5.0
Phase 2: • To assess the efficacy of LY3499446 alone or in combination with abemaciclib or erlotinib vs. docetaxel in patients with advanced *KRAS* G12C-mutant NSCLC. • To evaluate the efficacy of LY3499446 alone or in combination with cetuximab in patients with advanced *KRAS* G12C-mutant CRC. • To evaluate the efficacy of single-agent LY3499446 in patients with advanced *KRAS* G12C-mutant solid tumors (other than NSCLC and CRC).	• Per RECIST v1.1: o ORR (coprimary for NSCLC cohorts; primary for CRC cohorts and Other tumors cohort) o PFS (coprimary for NSCLC cohorts)
Secondary	
Phase 1 Dose Escalation: • To characterize the safety and toxicity profile of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib (NSCLC), or cetuximab (CRC) to patients with advanced solid tumors with *KRAS* G12C mutation. • To assess the PK of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation. • To assess any antitumor activity of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation.	• Safety as determined by (including but not limited to) TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0) • Plasma concentration of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab • Per RECIST v1.1: ORR, PFS, DoR, DCR
Phase 2: • To assess the efficacy of LY3499446 administered as monotherapy or in combination with abemaciclib or erlotinib in patients with NSCLC tumors harboring *KRAS* G12C mutations, and of LY3499446 administered as monotherapy or in combination with cetuximab in patients with CRC tumors harboring *KRAS* G12C mutations, and LY3499446 administered as monotherapy in patients with solid tumors, other than NSCLC and CRC, harboring *KRAS* G12C mutations. • To characterize the safety and toxicity profile of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab to patients with advanced solid tumors with *KRAS* G12C mutation. • To assess the PK of LY3499446 administered as monotherapy and in	• Per RECIST v1.1: o DoR, DCR, TTR, OS (all cohorts) o PFS (CRC cohorts and Other tumors) • Safety as determined by (including but not limited to) TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0) • Plasma concentration of LY3499446 administered as monotherapy and in combination with abemaciclib erlotinib, or cetuximab

combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation.	

Abbreviations: CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; NSCLC = nonsmall cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time to response.

Overall Design:

Study JZKA is a first in human, multicenter, open-label dose escalation Phase 1 study, followed by a cohort- and disease-specific randomized Phase 2, and a monotherapy Phase 2 expansion in patients with solid tumors harboring *KRAS* G12C mutations other than NSCLC and CRC.

The Phase 1 portion will enroll patients with *KRAS* G12C mutant solid tumors, where patients will be treated with monotherapy, or in combination with abemaciclib, erlotinib, or cetuximab.

Once a recommended phase 2 dose (RP2D) is established, patients with *KRAS* G12C mutant NSCLC will be randomized across 4 cohorts to evaluate for efficacy and safety to select the optimal regimen for further development. This part is a randomized, controlled, Phase 2 design.

For patients with *KRAS* G12C mutant CRC, patients will be randomized to either LY3499446 alone or in combination with cetuximab during the Phase 2 part.

For patients with *KRAS* G12C mutant solid tumors (other than NSCLC or CRC), an expansion cohort of LY3499446 monotherapy will proceed to assess the potential for efficacy once RP2D of LY3499446 monotherapy is established.

Disclosure Statement: This is an open-label, Phase1/2 study that consists of a dose escalation followed by a parallel-cohort randomization in patients harboring *KRAS* G12C mutations.

Number of Participants:

Approximately 111 to 135 (45 monotherapy, 22-30 per combination) patients will be enrolled in the Phase 1 portion of the study (including dose-escalation evaluations and backfills). Approximately 140 to 280 patients will be enrolled in the Phase 2 portion of the study.

- **Phase 1:** Total enrollment will be determined by the incidence of dose-limiting toxicities.
  - Monotherapy dose escalation (Part A): approximately 45 patients will be enrolled (including 10 patients per cohort as "backfill")
  - Combination dose escalation (Part B, C, and D): approximately 22 to 30 patients in each part will be enrolled (including 10 patients per cohort as "backfill")
- **Phase 2:** Approximately 140 to 280 patients will be enrolled into the Phase 2 portion of this study.
  - For patients with NSCLC: randomized design with docetaxel to establish efficacy and safety
    - Up to 160 patients in total will be enrolled and randomized at a 1:1:1:1 ratio to monotherapy (Cohort E1), combination with abemaciclib (Cohort E2), combination with erlotinib (Cohort E3), or docetaxel (Cohort E4). An interim data review will be performed based on efficacy, safety, and pharmacokinetics

(PK) data. Enrollment will continue while this analysis is being conducted. A final data review will be performed based on safety, efficacy, and PK data.

- For patients with CRC: randomized design for relative activity estimation
  - A total of approximately 40 to 80 patients will be enrolled across Cohorts F1 and F2. Initially, 40 patients will be randomized at a 1:1 ratio to monotherapy (Cohort F1) or combination with cetuximab (Cohort F2), and an interim data review will be performed based on safety, efficacy, and PK data.
  - After 40 patients are randomized, an interim analysis of safety and efficacy will occur. If 1 arm meets the criteria for futility, the corresponding arm will close, while the open arm may enroll an additional 20 patients. The "winning" arm should have demonstrated better efficacy signal in terms of superior overall response rate and comparable safety profile. A final data review will be performed based on safety, efficacy, and PK data. If no meaningful difference in efficacy or safety is observed between the 2 arms, approximately 80 total randomized patients (40 in each arm) will be enrolled.
- Other Tumors with *KRAS* G12C mutation (other than CRC and NSCLC) with monotherapy: approximately 40 patients will be enrolled in Cohort G, with interim data review performed after first 20 patients. The purpose of this portion is signal-finding.

Intervention Groups and Duration:

Patients enrolled in this study will receive LY3499446 monotherapy or in combination with abemaciclib, erlotinib, or cetuximab, as shown in the following table. In addition to the LY3499446 dose levels specified in the table below, intermittent dose levels, and/or alternative schedules may be explored in accordance with the dose finding rules. Similarly, lower doses or alternative schedules of abemaciclib and erlotinib may be explored below the currently approved doses based on emerging safety data. The planned duration of treatment is not fixed; participants will remain on study until disease progression or unacceptable toxicity occurs. If participants are discontinued from abemaciclib, erlotinib, or cetuximab therapy, they will be allowed to continue on LY3499446 treatment if receiving ongoing clinical benefit. However, if patients are discontinued from LY3499446 treatment, they will be allowed to continue on therapy with the respective combination drug per the investigator's discretion, with the exception of patients enrolled in the cetuximab cohorts (C1, C2, and F2).

Phase 1

	Study Drug(s) (Route of Administration)	Cohort	*Proposed* Doses	Dose Schedule
Monotherapy/ Part A	LY3499446 (PO)	A0[a]	CCI	QOD
		A1[b]	CCI	QD
		A2	CCI	BID
		A-1[c]	CCI	QD
Combination/ Part B/C/D	LY3499446 (PO)	B0/C0/D0	TBD	TBD
		B1/C1/D1	TBD	TBD
		B2/C2/D2	TBD	TBD
		B3/C3/D3	TBD	TBD
		B-1/C-1/D-1	TBD	TBD
	Abemaciclib (PO)	B0/B1/B2/B3	150 mg	BID
		B-1	100 mg	BID
	Cetuximab (IV)	C0/C1/C2/C3	400 mg/m^2 C1D1; 250 mg/m^2	QW
		C-1	400 mg/m^2 C1D1; 250 mg/m^2	QW
	Erlotinib (PO)	D0/D1/D2/D3	150 mg	QD
		D-1	100 mg	QD

Abbreviations: BID = twice daily; IV = intravenously; PO = orally; QD = once daily; QOD = once every other day;TBD = to be determined.

[a] In the event the CCI dosing also leads to CCI or other dose-limiting toxicities, lower doses and other dosing frequencies may be explored to ensure patient safety and sufficient target engagement for clinical benefit. These may include, for example, dose level A-1 of CCI or CCI.

[b] In the event the CCI dosing should lead to CCI or other dose-limiting toxicities, a dose of CCI may be explored to ensure patient safety and sufficient target engagement for clinical benefit. As warranted by data, an intermediate dose, for example CCI may be explored.

[c] In the event the CCI dose should lead to CCI or other dose-limiting toxicities, a dose of CCI may be explored to ensure patient safety and sufficient target engagement for clinical benefit.

Phase 2

	Study Drug(s) (Route of Administration)	Cohort	*Proposed* Doses	Dose Schedule
Monotherapy	LY3499446 (PO)	E1/F1/G	$RP2D_M$	TBD
Combination with Abemaciclib	LY3499446 (PO)	E2	$RP2D_A$	TBD
	Abemaciclib (PO)	E2	150 mg	BID
Combination with Erlotinib	LY3499446 (PO)	E3	$RP2D_E$	TBD
	Erlotinib (PO)	E3	150mg	QD
Combination with Cetuximab	LY3499446 (PO)	F2	$RP2D_C$	TBD
	Cetuximab (IV)	F2	400 mg/m^2 C1D1; 250 mg/m^2	QW
Active Comparator	Docetaxel (IV)	E4	75 mg/m^2	Q3W

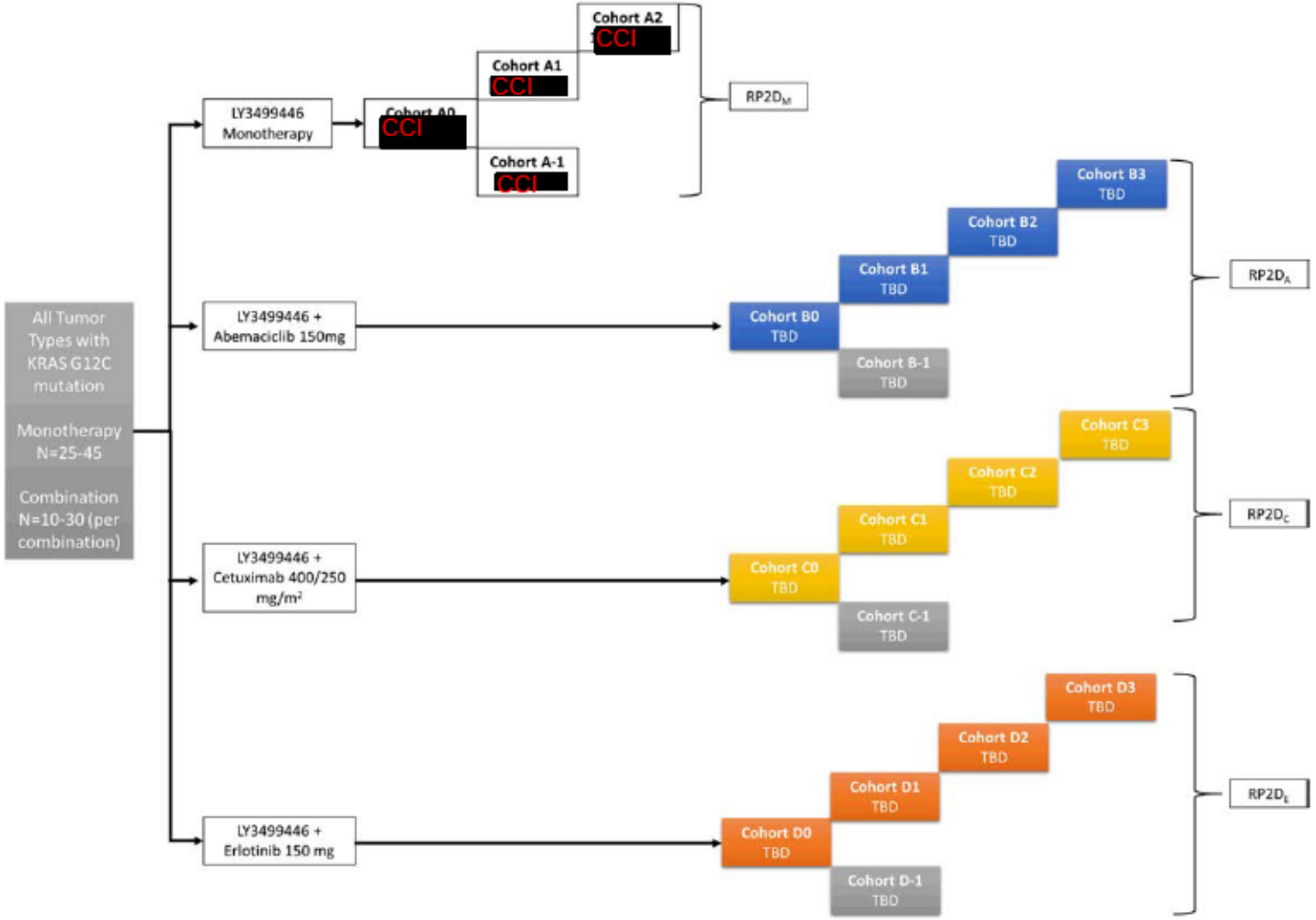
Abbreviations: BID = twice daily; DL = dose level; IV = intravenous; PO = orally; QD = daily; QW = every week; Q3W = every 3 weeks; $RP2D_A$ = abemaciclib recommended phase 2 dose; $RP2D_C$ = cetuximab recommended phase 2 dose; $RP2D_E$ = erlotinib recommended phase 2 dose; $RP2D_M$ = monotherapy recommended phase 2 dose.

Note: lower doses or alternative schedules of abemaciclib and erlotinib may be explored below the currently approved doses based on emerging safety data.

Data Monitoring Committee: No

1.2. Schema

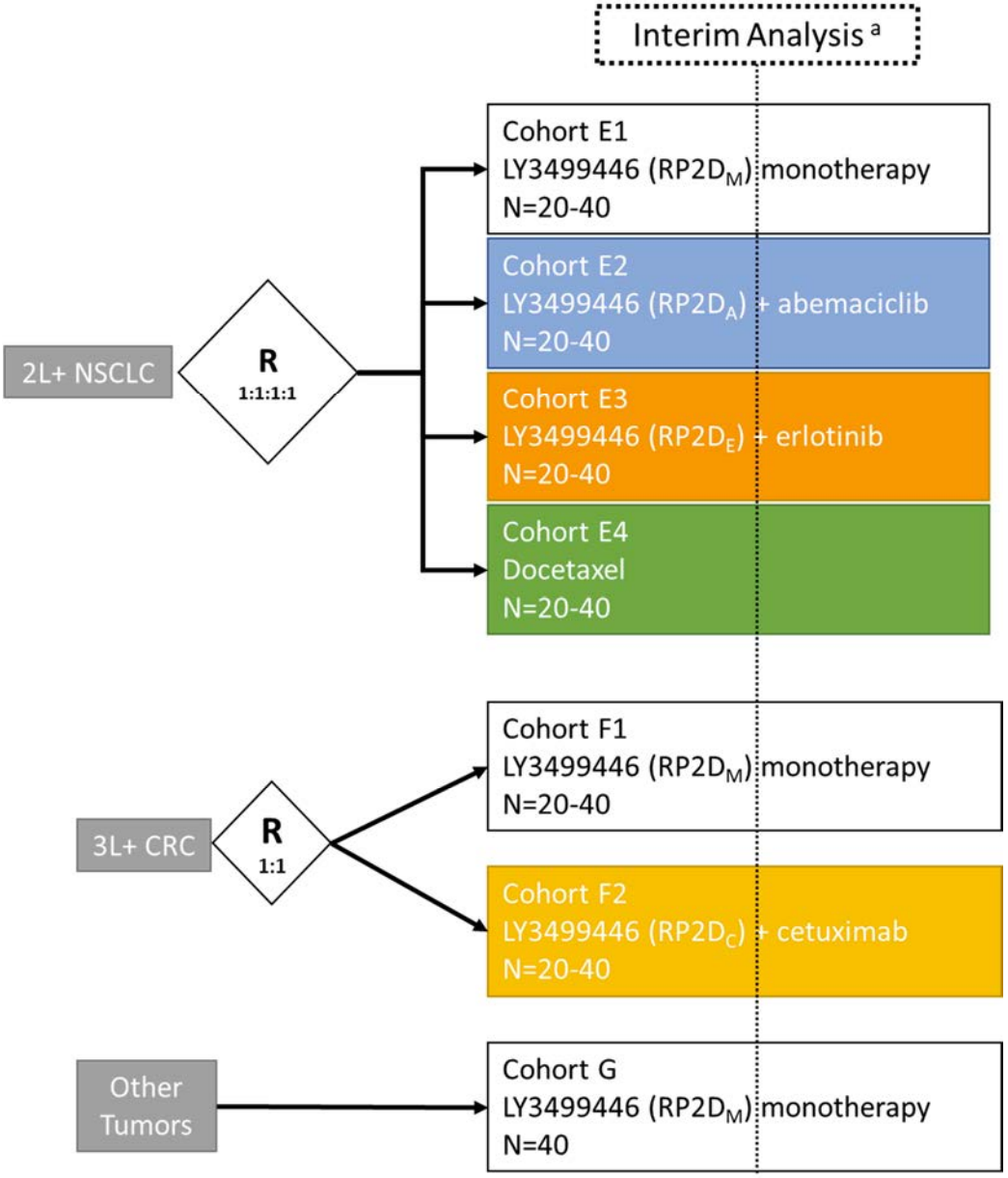
1.2.1. Phase 1 Schema



Abbreviations: BID = twice daily; DLT = dose-limiting toxicity; N = number of patients; PK = pharmacokinetics; PO = orally; $RP2D_A$ = recommended phase 2 dose in combination with abemaciclib; $RP2D_C$ = recommended phase 2 dose in combination with cetuximab; $RP2D_E$ = recommended phase 2 dose in combination with erlotinib; $RP2D_M$ = monotherapy recommended phase 2 dose.

Note: Dose de-escalation cohorts will only occur if the initial LY3499446 doses are determined to be intolerable. In addition to the LY3499446 dose levels specified in this figure, intermittent dose levels, or alternative schedules may be explored. Similarly, lower doses or alternative schedules of abemaciclib and erlotinib may be explored below the currently approved doses based on emerging safety data. The totality of data including safety, and PK exposure and the incidence of DLT may help guide evaluating alternative dosing and schedule (e.g. CCI vs CCI).

1.2.2. Phase 2 Schema



Abbreviations: 2L+ = 2 or more lines of therapy; 3L+ = 3 or more lines of therapy; CRC = colorectal cancer; N = number of patients; NSCLC = non-small cell lung cancer; R = randomization; $RP2D_A$ = recommended phase 2 dose in combination with abemaciclib; $RP2D_C$ = recommended phase 2 dose in combination with cetuximab; $RP2D_E$ = recommended phase 2 dose in combination with erlotinib; $RP2D_M$ = monotherapy recommended phase 2 dose.

[a] An interim analysis will take place after approximately 20 patients have been enrolled within each cohort. See Section 9.5.

1.3. Schedule of Activities (SoA)

This section contains the following schedules:

- Schedule for Participants Enrolled in Phase 1
- Schedule for Participants Enrolled in Phase 2
- Continued Access Schedule for All Participants
- Sampling Schedule for PK and electrocardiograms for All Participants

Schedule for Participants Enrolled in Phase 1

Screening, On-Study, and Posttreatment SoA																		
	Screening		**On-Treatment Cycle = 21 days**													**Posttreatment**		**Instructions**
			Cycle 1						**Cycle 2**						**Cycle 3-n**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	
	(Day Relative to C1D1)		(±1 days)						(±1 days)						(±1 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤14**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**V801**	**V802-8XX**	
Procedure																		
Informed consent	X																	ICF must be signed before any protocol-specific procedures are performed.
Inclusion/ exclusion criteria		X																
Medical history	X																	Including assessment of pre-existing conditions and historical illnesses, pre-existing toxicities from prior therapies, and habits (such as tobacco and alcohol use).
Cancer treatment history	X																	Record prior anticancer therapy.

Screening, On-Study, and Posttreatment SoA																		
	Screening		**On-Treatment Cycle = 21 days**													**Posttreatment**		
			Cycle 1						**Cycle 2**						**Cycle 3-n**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	**Instructions**
	(Day Relative to C1D1)		(±1 days)						(±1 days)						(±1 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤14**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**V801**	**V802-8XX**	
Procedure																		
Concomitant medication	X		See Instructions													X		• At baseline, record prior and concurrent medications. • Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.
Physical examination	X		X		X		X		X						X	X		
Vital signs	X		X		X		X		X		X		X		X	X		Measure vital signs (height [at baseline], weight, temperature, blood pressure, pulse rate, and SpO2).
AE collection	X		See Instructions													X		• Collect continuously at every visit and throughout the study. • CTCAE Version 5.0
ECOG PS	X		X						X						X	X		During study treatment, perform ≤3 days prior to treatment.

Screening, On-Study, and Posttreatment SoA																		
	Screening		**On-Treatment Cycle = 21 days**													**Posttreatment**		
			Cycle 1						**Cycle 2**						**Cycle 3-n**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	**Instructions**
	(Day Relative to C1D1)		(±1 days)						(±1 days)						(±1 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤14**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**V801**	**V802-8XX**	
Procedure																		
ECG		X	See Section 1.3.1															At baseline (screening): Single local ECG with central storage. Must be collected before first dose and any blood draws. Participant should be supine for 5 to 10 minutes before collection and remain supine during ECG. On-study: Triplicate ECGs with digital data. Participant should be supine for 5 to 10 minutes before collection and remain supine during ECG. Local testing with central storage.
Hematology		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		May be collected ±1 day from scheduled visit. See Appendix 2
Coagulation		X																See Appendix 2. Perform at baseline and as clinically indicated
Clinical chemistry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		May be collected ±1 day from scheduled visit. See Appendix 2
Urine sample					X													Collect urine sample starting at the time of dose and completed collection at 12 hours.
Urinalysis		X	X		X		X		X		X		X		X	X		See Appendix 2.
Thyroid function		X																May be collected ±3 days from scheduled visit. See Appendix 2.

Screening, On-Study, and Posttreatment SoA																		
	Screening		**On-Treatment Cycle = 21 days**													**Posttreatment**		
			Cycle 1						**Cycle 2**						**Cycle 3-n**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	**Instructions**
	(Day Relative to C1D1)		(±1 days)						(±1 days)						(±1 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤14**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**V801**	**V802-8XX**	
Procedure																		
Pregnancy test		X	See Instructions													X		Applies only to WOCBP. See Appendix 2. **Note:** during study treatment, perform monthly (±3 days) or as required per local regulations and/or institutional guidelines.
Radiologic imaging and measurement of palpable or visible lesions	X		See Instructions													X		Perform according to RECIST v1.1 criteria, by the same method used at baseline, every 6 weeks (±7 days) for the first 6 months, then every 9 weeks (±7 days) until radiographic disease progression, death, or study completion, whichever occurs first. Perform as scheduled, even if study treatment is delayed or omitted. Centrally collected and stored.
Brain MRI/CT	X																	Only for patients with NSCLC and as clinically indicated for patients with other tumor types
Survival assessment																X	X	Perform every 3 months (±7 days). If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.

Screening, On-Study, and Posttreatment SoA																	
	Screening		**On-Treatment Cycle = 21 days**												**Posttreatment**		
			Cycle 1						**Cycle 2**						**Cycle 3-n**	**Short-Term Follow-Up[a]**	**Long-Term Follow-Up[b]**	**Instructions**
	(Day Relative to C1D1)		(±1 days)						(±1 days)						(±1 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤14**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**D4**	**D8**	**D11**	**D15**	**D18**	**D1**	**V801**	**V802-8XX**	
Procedure																		
Collection of poststudy-treatment anticancer therapy information																X	X	Discontinuation from study must occur prior to introduction of the new agent.
Patient diary			See Instructions															Provide patient diary Day 1. Completed QD by patient. Review at each study visit for first 2 cycles.
PK			See Section 1.3.1															Refer to Section 1.3.1 for PK sampling time points.
Whole blood (PGx)			X															Collect once. Sample can be collected at any time if not collected on C1D1.
Biomarker plasma			X Predose						X						X	X		C1D1 sample: collect prior to initiating treatment. Collect on day 1 of every odd cycle starting at C3D1.
Administer LY3499446			See Instructions															Administer per RP2D. See Section 6.1.
Administer abemaciclib			See Instructions															Administer BID according to Section 6.1.
Administer cetuximab			See Instructions															Administer by IV QW starting on C1D1.According to Section 6.1.
Administer erlotinib			See Instructions															Administer 150 mg QD. See Section 6.1.

Abbreviations: AE = adverse event; BID = twice daily; C = cycle; CR = complete response; CRC = colorectal cancer; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ICF = informed consent form; IV = intravenous; MRI = magnetic resonance imaging; NSCLC = nonsmall cell lung cancer; PGx = pharmacogenomics; PK = pharmacokinetics; PO = orally; Q3W = every 3 weeks; QD = daily; RECIST = Response Evaluation Criteria in Solid Tumors; SoA = schedule of activities; V = visit; V8XX = follow-up visit number; WOCBP = women of childbearing potential.

[a] Short-term follow-up begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.

[b] Long-term follow-up occurs every 3 months for the first 2 years and every 6 months thereafter and begins when short-term follow-up period is completed and continues until death or study completion. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent/assent unless he or she has explicitly provided permission and consent/assent.

Schedule for Participants Enrolled in Phase 2

Screening, On-Study, and Posttreatment SoA

	Screening		On-Treatment Cycle = 21 days							Posttreatment		Instructions
	(Day Relative to C1D1)		Cycle 1			Cycle 2			Cycle 3-n	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
			(±3 days)			(±3 days)			(±3 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure												
Informed consent	X											ICF must be signed before any protocol-specific procedures are performed.
Inclusion/exclusion criteria		X										
Medical history	X											Including assessment of pre-existing conditions and historical illnesses, pre-existing toxicities from prior therapies, and habits (such as tobacco and alcohol use).
Cancer treatment history	X											Record prior anticancer therapy.
Concomitant medication	X		See Instructions							X		• At baseline, record prior and concurrent medications. • Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.
Physical examination	X		X			X			X	X		
Vital signs	X		X			X			X	X		Measure vital signs (height [at baseline], weight, temperature, blood pressure, pulse rate, and SpO2).
AE collection	X		See Instructions							X		• Collect continuously at every visit and throughout the study. • CTCAE Version 5.0.
ECOG PS	X		X			X			X	X		During study treatment, perform ≤3 days prior to treatment.
ECG		X	See Section 1.3.1									At baseline (screening): Single local ECG. Must be collected before first dose and any blood draws. Participant should be supine for

Screening, On-Study, and Posttreatment SoA												
	Screening		On-Treatment Cycle = 21 days							Posttreatment		Instructions
	(Day Relative to C1D1)		Cycle 1			Cycle 2			Cycle 3-n	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
			(±3 days)			(±3 days)			(±3 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure												
												5 to 10 minutes before collection and remain supine during ECG. On-study: Single ECGs. Participant should be supine for 5 to 10 minutes before collection and remain supine during ECG. Local testing.
Hematology		X	X			X			X	X		May be collected ±3 days from scheduled visit. See Appendix 2.
Coagulation		X										See Appendix 2. Perform at baseline and as clinically indicated.
Clinical chemistry		X	X			X			X	X		May be collected ±3 days from scheduled visit. See Appendix 2.
Urine sample				X								Collect urine sample starting at the time of dose and completed collection at 12 hours.
Urinalysis		X	X			X			X	X		See Appendix 2. Perform at baseline and as clinically indicated.
Thyroid function		X										May be collected ±3 days from scheduled visit. See Appendix 2.
Pregnancy test		X	See Instructions							X		Applies only to WOCBP. See Appendix 2. **Note:** during study treatment, perform monthly (±3 days) or as required per local regulations and/or institutional guidelines.

Screening, On-Study, and Posttreatment SoA												
	Screening		On-Treatment Cycle = 21 days							Posttreatment		Instructions
	(Day Relative to C1D1)		Cycle 1			Cycle 2			Cycle 3-n	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
			(±3 days)			(±3 days)			(±3 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure												
Radiologic imaging and measurement of palpable or visible lesions	X		See Instructions							X		Perform according to RECIST v1.1 criteria, by the same method used at baseline, every 6 weeks (±7 days) for the first 6 months, then every 9 weeks (±7 days) until radiographic disease progression, death, or study completion, whichever occurs first. Perform as scheduled, even if study treatment is delayed or omitted. Centrally collected and stored.
Brain MRI/CT	X											
Survival assessment										X	X	Perform every 3 months (±7 days). If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
Collection of poststudy-treatment anticancer therapy information										X	X	Discontinuation from study must occur prior to introduction of the new agent.
Patient diary			See Instructions									Provide patient diary D1. Completed QD by patient. Review at each study visit for first 2 cycles.
PK			See Section 1.3.1									Refer to Section 1.3.1 for PK sampling time points.
Whole Blood (PGx)			X									Collect once. Sample can be collected at any time if not collected on C1D1.

Screening, On-Study, and Posttreatment SoA												
	Screening		On-Treatment Cycle = 21 days							Posttreatment		Instructions
	(Day Relative to C1D1)		Cycle 1			Cycle 2			Cycle 3-n	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
			(±3 days)			(±3 days)			(±3 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure												
Biomarker plasma			X (Predose)			X			See Instructions	X		C1D1 sample: collect prior to initiating treatment. Plasma samples from C3D1 onward to be collected on D1 of each odd cycle.
Biomarker serum (Cohorts F1 & F2 – CRC participants)			X (Predose)	X	X							• C1D1 sample collect prior to initiating treatment.
Tumor biopsy (Cohorts E1, E2, E3, E4 - NSCLC participants)	X					X				Optional X		• Collect at baseline (prior to initiating treatment). • Second biopsy collect on C2D1 (±3 days). • Archival tumor may be requested if new baseline insufficient tumor quantity/quality. • Optional new tumor biopsy at progression for patients on study for at least 6 months who have partial or CR.
Tumor biopsy (Cohort F1 – CRC monotherapy participants)	X					X				Optional X		• Collect at baseline (prior to initiating treatment) • Second biopsy collect on C2D1 (±3 days). • Archival tumor may be requested if new baseline biopsy has insufficient tumor quantity/quality. • Optional new tumor biopsy at progression for patients on study for at least 6 months who have partial or CR.

Screening, On-Study, and Posttreatment SoA												
	Screening		On-Treatment Cycle = 21 days							Posttreatment		Instructions
	(Day Relative to C1D1)		Cycle 1			Cycle 2			Cycle 3-n	Short-Term Follow-Up[a]	Long-Term Follow-Up[b]	
			(±3 days)			(±3 days)			(±3 days)	(±3 days)	(±7 days)	
Visit	**≤28**	**≤7**	**D1**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure												
Tissue biopsy (Cohort F2 - CRC combination therapy participants)			See Instructions							Optional X		• Initial biopsy: collect 1 week post monotherapy lead-in (day 5, 6, or 7) • Second biopsy: collect on C2D1 (±3 days). • Optional new tumor biopsy at progression for patients on study for at least 6 months who have partial or CR.
Archival tissue (Cohort F2 & G)	X											• If archival tissue not available or insufficient, new baseline biopsy required.
Administer LY3499446			See Instructions									Administer PO BID according to Section 6.1.
Administer abemaciclib			See Instructions									Administer PO BID according to Section 6.1.
Administer cetuximab			See Instructions									Administer by IV QW according to Section 6.1.
Administer erlotinib			See Instructions									Administer 150 mg QD. See Section 6.1.
Administer docetaxel			See Instructions									Administer 75 mg/m^2 Q3W. See Section 6.1.

Abbreviations: AE = adverse event; BID = twice daily; C = cycle; CR = complete response; CRC = colorectal cancer; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; ICF = informed consent form; IV = intravenous; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; PGx = pharmacogenomics; PK = pharmacokinetics; PO = orally; Q3W = every 3 weeks; QD = daily; QW = every week; RECIST = Response Evaluation Criteria in Solid Tumors; SoA = schedule of activities; V = visit; V8XX = follow-up visit number; WOCBP = women of childbearing potential.

[a] Short-term follow-up begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.

[b] Long-term follow-up occurs every 3 months for the first 2 years and every 6 months thereafter and begins when short-term follow-up period is completed and continues until death or study completion. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent/assent unless he or she has explicitly provided permission and consent/assent.

Continued Access SoA for All Participants

Visit[a]	Study Treatment	30-Day Follow-Up	Instructions
	501-5XX	901	
Procedure			
AE Collection	X	X	Per CTCAE v5.0, for post follow-up, the investigator should only be made aware of collected SAEs related to study regimen or protocol procedures. Collect throughout the study.
Administer study intervention	X		See Section 6.1 for Study Intervention administration details and guidelines.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event; SoA = schedule of activities.

[a] Continued access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

1.3.1. Sampling Schedule for PK and ECGs for Participants in Phase 1

Cycle	Day	Dose	Time after Dose (hours)[a]	LY3499446	Combination Agent[b]	Collect ECG[d]
1	1	1	Predose	X		X[e]
			0.5	X ±5 min		X ±5 min
			1	X ±10 min		X ±10 min
			1.5	X ±10 min		
			2	X ±10 min		
			3	X ±10 min		
			4	X ±20 min	Erlotinib[c] Cetuximab[c]	X ±20 min
			8	X ±30 min	Abemaciclib[c]	X ±30 min
			24 (Predose, if applicable)	X ±60 min		
	8 (±1 day, to align with LY3499446 dosing day)	1	Predose	X		X[e]
			0.5	X ±5 min		X ±5 min
			1	X ±10 min		X ±10 min
			1.5	X ±10 min		
			2	X ±10 min		
			3	X ±10 min		
			4	X ±20 min	Erlotinib[c] Cetuximab[c]	X ±20 min
			8	X ±30 min	Abemaciclib[c]	X ±30 min

Cycle	Day	Dose	Time after Dose (hours)[a]	LY3499446	Combination Agent[b]	Collect ECG[d]
2 and every other cycle	1	1	Predose	X		X[e]
			4	X ±20 min	Erlotinib[c] Cetuximab[c] Abemaciclib[c]	X ±20 min

Abbreviations: ECG = electrocardiogram; PK = pharmacokinetics.

[a] Time after dose starts after the patient has ingested the full amount of the capsules.

[b] Combination agent samples are to be collected only if the patient is being treated by that agent.

[c] PK sample collection timepoint for combination agent is intended to capture C_{max}.

[d] All ECGs (excluding screening and follow-up ECGs) are to be triplicate ECGs; the 3 replicates of each should be completed within 5 minutes and preferably 1 minute apart.

[e] Predose ECGs should be taken at either 90 (-90) minutes, 60 (-60) minutes, or 30 (-30) minutes. Predose timepoints are flexible for site convenience

1.3.2. Sampling Schedule for PK and ECGs for Participants in Phase 2

Phase 2 PK sampling schedule is subject to change based on PK data and analysis results from the Phase 1 potion of the study.

Cycle	Day	Dose	Time after Dose (hours)[a]	LY3499446	Combination Agent[b]	Collect ECG[d]
1	1	1	Predose	X		X[e]
			1	X		X ±30 min
			4	X	Erlotinib[c]	
			8	X	Abemaciclib[c]	
2	1	1	Predose	X	Erlotinib[c] Cetuximab[c] Abemaciclib[c]	X[e]
			0.5	X		
			1	X		X ±30 min
			4	X		
3 and every other cycle	1	1	Predose	X	Cetuximab[c] Erlotinib[c] Abemaciclib[c]	X[e]
			1	X		X ±30 min

Abbreviations: C_{max} = maximum concentration; ECG = electrocardiogram; PK = pharmacokinetics.

[a] Time after dose starts after the patient has ingested the full amount of the capsules.

[b] Combination agent samples are to be collected only if the patient is being treated by that agent.

[c] PK sample collection timepoint for combination agent is intended to capture C_{max}.

[d] All ECGs in Phase 2 should be single ECGs

[e] Predose ECGs should be taken at either 90 (-90) minutes, 60 (-60) minutes, or 30 (-30) minutes. Predose timepoints are flexible for site convenience.

2. Introduction

2.1. Study Rationale

More than 30% of all cancer types possess mutations in RAS. *KRAS* mutations account for approximately 85% of RAS-associated cancers in humans and have typically been associated with worse overall survival (OS) and increased resistance to treatments compared to *KRAS* wild-type tumors (Dinu et al. 2014; Ferrer et al. 2018; Windon et al. 2018). *KRAS* mutations occur in approximately 16% to 40% of nonsmall cell lung cancer (NSCLC), and G12C mutations represent approximately 40% of total mutations in NSCLC (Fernández-Medarde and Santos 2011). However, due to its lack of deep pockets for binding of small molecule inhibitors, RAS is typically deemed as "undruggable." Various anti-RAS therapeutic strategies have been proven largely ineffective (Ferrer et al. 2018; Ramon et al. 2018; O'Bryan 2019). Recent studies have been focusing on *KRAS* mutation-specific therapies.

LY3499446 is a potent and orally (PO) available small molecule inhibitor of KRAS G12C, CCI and has demonstrated significant activity in preclinical models against a wide range of *KRAS* G12C mutant tumors.

Study J2K-MC-JZKA (JZKA) consists of a Phase 1, open-label, dose-escalation study of LY3499446 as monotherapy or in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation followed by a randomized, controlled, Phase 2 study of LY3499446 administered as monotherapy or in combination with abemaciclib, erlotinib, or standard of care, docetaxel, in patients with NSCLC tumors harboring *KRAS* G12C mutations (Cohorts E1 through E4), and of LY3499446 administered as monotherapy or in combination with cetuximab in patients with colorectal cancer (CRC) harboring *KRAS* G12C mutations (cohorts F1 and F2), and an expansion of LY3499446 administered as monotherapy in patients with *KRAS* G12C mutant solid tumors (Cohort G), other than NSCLC and CRC.

2.2. Background

The *RAS* family of genes, including *KRAS*, *HRAS*, and *NRAS*, are the most common oncogenes in cancer (Lindsay et al. 2018), with approximately 30% of all human tumor types possessing mutations in RAS (O'Bryan 2019). RAS proteins function as a GTPase and have a central coordinating role connecting upstream signals from cell surface receptors to downstream signaling pathways associated with cancer (Lindsay et al. 2018). Typically, RAS proteins stay in a GDP-bound inactive form in quiescent cells. The downstream signaling is activated when GDP is released from RAS via the action of guanine exchange factors and subsequently binds to guanosine triphosphate (GTP) with high specificity and affinity. The exchange of GDP for GTP leads to characteristic changes in RAS conformation, resulting in recruitment of downstream effector proteins, such as RAF and PI3K, and activation of key signaling pathways.

Among all *RAS* genes, *KRAS* mutations account for approximately 85% of *RAS*-associated cancers in humans: about 90% of pancreatic cancers (Zeitouni et al. 2016), 35% to 45% of CRC

(Tan and Du 2012; Wilson et al. 2016), and 25% NSCLC (Román et al. 2018). *KRAS* mutations are well-characterized oncogenic drivers and have typically been associated with worsened OS and increased resistance to treatments than *KRAS* wild-type tumors (Dinu et al. 2014; Ferrer et al. 2018; Windon et al. 2018). Most *KRAS* mutations affect exon 2 (codon 12/13) and exon 3 (codon 61), leading to KRAS remaining in the GTP-bound active form (Román et al. 2018). Evidence suggests variability in biological activity across *KRAS* mutant cancers. In patients with NSCLC, the presence of *KRAS* G12C mutation in resected tumors was associated with worse disease-free survival and OS compared to other *KRAS* mutations and to *KRAS* wild-type (Nadal et al. 2014). *KRAS* G12C accounts for 12% of all *KRAS* mutations and 40% of *KRAS* mutations in NSCLC (Fernández-Medarde and Santos 2011; Prior et al. 2012). The overall prevalence of *KRAS* G12C in NSCLC is about 10% to 16%, and 1% to 4% in colorectal and pancreatic cancers, respectively (Bailey et al. 2016; Campbell et al. 2016; Giannakis et al. 2016; Jordan et al. 2017).

RAS has been a target for therapeutic inhibition for the past 3 decades (Wilson et al. 2016). However, due to its lack of deep pockets for binding of small molecule inhibitors, RAS is typically deemed as "undruggable" (O'Bryan 2019). Various therapeutic strategies, including targeting KRAS membrane association, targeting downstream effectors of KRAS pathways, and inhibition of synthetic lethal targets, have been investigated in both preclinical and clinical settings and have, with some notable exceptions, proven ineffective (Ferrer et al. 2018; Román et al. 2018; O'Bryan, 2019). In the SELECT-1 Phase 3 study, adding MEK inhibitor selumetinib to docetaxel did not show significant improvement in progression-free survival (PFS) or OS in second-line advanced NSCLC patients with *KRAS* mutations: median PFS was 3.9 months with selumetinib plus docetaxel compared to 2.8 months with docetaxel alone (hazard ratio [HR], 0.93) with a median OS of 8.7 months and 7.9 months (HR 1) and an overall response rate (ORR) of 20.1% and 13.7%, respectively (Jänne et al. 2017).

Despite the efforts over the past 3 decades, there are no therapeutic agents approved by the United States Food and Drug Administration (FDA) targeting *RAS* mutations. Current approaches to treating NSCLC and CRC patients with *KRAS* mutations include standard chemotherapy or immunotherapy, if applicable (Aredo and Padda 2018). Responses are variable across different patient subsets, highlighting the challenges in developing effective therapy for patients with *KRAS* mutant NSCLC, and such therapy is not directed specifically at *KRAS* mutations (Kim et al. 2017; Rittmeyer et al. 2017). For CRC patients with *KRAS* mutations, chemotherapy alone or in combination with antiangiogenic therapy is standard-of-care in first- and second-line therapy with initially good response to therapy followed universally by progression. Upon progression, therapy with either regorafenib or trifluridine plus tipiracil is preferred and represents current standard-of-care in third-line therapy, regardless of *RAS* mutation status (Grothey et al. 2013; Mayer et al. 2015). In the CORRECT study (Grothey et al. 2013), median OS for all previously treated CRC patients (including about 50% to 60% of patients with known *KRAS* mutations) was 6.4 months in the regorafenib group, with a response rate of 1% and median PFS of 1.9 months, indicating the inadequacy of current systemic therapy and high unmet medical need.

Nonetheless, a new wave of development of anti-KRAS therapies has been stimulated by recent research findings, particularly focusing on *KRAS* mutation-specific therapies. These therapies include molecules targeting the inactive form of KRAS trapped in GDP-bound form and

demonstrate activity in preclinical models (Ostrem et al. 2013; Lito et al. 2016; Particelli et al. 2016; Janes et al. 2018).

These preclinical observations were further supported by a recent disclosure on an ongoing Phase 1 study (Fakih et al. 2019) evaluating the safety and tolerability of a KRAS G12C inhibitor, AMG510. Thirty-five patients with various locally advanced or metastatic solid tumors with *KRAS* G12C mutations (14 NSCLC, 19 CRC, and 2 with appendiceal cancer) were treated. The toxicity profile was favorable with no observed dose-limiting toxicity (DLT) at the dose levels (DLs) tested (180 to 960 mg, daily [QD]) and preliminary results indicated a potential for antitumor activity when administered as a monotherapy based on a 50% (5/10) response rate seen in NSCLC patients (Fakih et al. 2019). Early clinical activity in CRC appears more limited with a majority (13/18) of evaluable CRC patients showing no objective response, albeit without overt disease progression. These findings provide a proof of concept that KRAS G12C can be targeted effectively and provide evidence of potential clinical utility of a KRAS G12C inhibitor given alone or in combination in the treatment of cancers that carry a *KRAS* G12C mutation.

Additionally, the development and approval of several targeted therapies across multiple tumor types highlighted several facts, especially in the context of targeting the RAS/RAF/MEK pathway:

1) there is potential for innate and acquired resistance in most patients (Prahallad et al. 2012; Van Emburgh et al. 2016)
2) there is variable activity across different tumor types based on histology, which has been clearly demonstrated in the case of *BRAF* V600E mutations in CRC, melanoma and NSCLC (Sosman et al. 2012; Bendell et al. 2014; Planchard et al. 2016)
3) combination therapies may have the potential to overcome innate resistance and delay emerging resistance as evidenced by data obtained in relevant preclinical models and clinical outcomes seen by combination therapy targeting the RAS/RAF/MEK pathway (Bendell et al. 2014; Long et al. 2014; Kopetz et al. 2015; Kopetz et al. 2017, ESMO 2019).

Mutations in the RAS/RAF pathway have remained a challenge for single agent-based regimens due to a compensatory mechanism leading to rapid evolution of acquired resistance (Villanueva et al. 2010; Prahallad et al. 2012; Wagle et al. 2014; Ahronian et al. 2015). This has been demonstrated clinically with *BRAF* V600E mutant NSCLC where the combination of BRAF and MEK inhibitors was more effective than the single agent (Planchard et al. 2016). Similarly, a triple combination of epidermal growth factor receptor (EGFR)/MEK/BRAF inhibitors was superior to standard-of-care in *BRAF* V600E mutant CRC (Kopetz et al. 2019). While further and more thorough studies are needed, in patients with *KRAS* G12C mutant CRC at least, the lack of objective response seen on treatment with AMG510 suggests that combination therapy may still be required with KRAS G12C targeted therapy in this setting, and possibly others.

LY3499446 is a potent and PO available small molecule inhibitor of KRAS G12C, CCI [redacted]

Abemaciclib is an inhibitor of cyclin-dependent kinase (CDK)4 and CDK6 and was most active against cyclin D1/CDK4 in enzymatic assays. Cyclin-dependent kinases CDK4 and CDK6 participate in a complex with D type cyclins to initiate the transition through the G1 restriction point. Cyclin-dependent kinase inhibitors p15INK4b and p16INK4a, the retinoblastoma tumor suppressor protein, and cyclin D family members are among the major regulatory genes of the G1/S transition. Overexpression of cyclin D1, abnormal RB1 pathway functioning, and mutated or aberrant $p16^{INK4a}$ have been reported in lung cancer (Zhou et al. 2001). In KRAS-positive NSCLC, constitutive KRAS activity can lead to abnormally increased levels of cyclin D, further increasing the pool of cyclin D accumulation (Coleman et al. 2004; Musgrove et al. 2011; Dempsey et al. 2013). Importantly, synthetic lethal interaction between *KRAS* mutation and CDK4 inhibition indicates a potential therapeutic application for CDK4 and CDK6 inhibitors in NSCLC (Puyol et al. 2010). Inhibition of CDK4 and CDK6 kinase activity by abemaciclib inhibits growth of human NSCLC tumor xenograft models in vivo (Patnaik et al. 2016).

The phase 3 study JUNIPER compared abemaciclib to erlotinib in previously treated advanced NSCLC patients with *KRAS* mutations (*KRAS* G12C represented 30%) (Goldman et al. 2018). Nearly 50% of patients in this study had tested positive for the presence of a *KRAS* G12C mutation. Median OS was 7.4 months with abemaciclib versus 7.8 months with erlotinib (HR 0.97), while PFS was 3.6 months versus 1.9 months (HR 0.58; $p<0.001$) with an ORR of 8.9% compared to 2.7% ($p=0.01$) (Goldman et al. 2018). Notably, the results in the G12C subgroup did not significantly differ from the overall or nonG12C subsets.

While the JUNIPER study did not meet its primary endpoint, additional preclinical mechanistic and combination data support the rationale for combining LY3499446 with abemaciclib. Along with our preclinical data demonstrating synergistic activity, Lou and colleagues demonstrated in CRISPER screen the possibility of synthetic lethal interaction of CDK4/6 inhibition with *KRAS* G12C (Lou et al. 2019). Additionally, the combination of the KRAS G12C inhibitor ARS-1620 with CDK4/6i demonstrated activity in pancreatic and lung cancer xenograft models. This data, along with our preclinical studies, provides the foundation to re-evaluate abemaciclib in combination with LY3499446 in *KRAS* G12C mutant NSCLC.

Preclinical studies of LY3499446 in combination with abemaciclib in vitro and in vivo in *KRAS* G12C mutant models demonstrated that LY3499446 is generally active in a panel of 18 *KRAS* G12C mutant cell lines consisting of lung, pancreatic, colorectal, esophageal, and bladder cancer cells with a range of the sensitivity in in vitro cell proliferation assay. In vitro combination of LY3499446 and abemaciclib shows synergistic or additive effects on inhibition of cell proliferation in such cell panels based on IC_{50} and combination index results . The synergistic effect was more significant for tumor cells, such as H1792, LXFA-983L and SW1573 less sensitive to LY3499446 monotherapy. In xenograft or patient-derived xenograft models of lung, colorectal, and pancreatic cancer, LY3499446 monotherapy demonstrated significant antitumor growth activity. However, the combination of LY3499446 and abemaciclib showed more robust antitumor growth activity based on tumor growth inhibition and regression .

Erlotinib is an EGFR small molecule inhibitor that was approved for treatment of patients with locally advanced or metastatic NSCLC, and patients with locally advanced, unresectable, or metastatic pancreatic cancer. LY3499446 binds to the GDP-bound and inactive form of KRAS protein. Although the *KRAS* G12C mutation impairs the GTPase activity of KRAS, the GTPase cycle through transition of GDP-bound inactive form to GTP-bound active bound form is still

essential for full function of KRAS G12C protein (Lito et al. 2016). Guanine nucleotide exchange factors (GEF), such as SOS, are important components critical for KRAS GDP to KRAS GTP transition. Epidermal growth factor receptor activation was demonstrated to enhance GEF activity, regulate KRAS GDP/GTP equilibrium, and thus impact the KRAS inhibition by a KRAS G12C inhibitor in *KRAS* G12C mutant cells (Lito et al. 2016; Lou et al. 2019). Additionally, EGFR is often expressed and activated in tumor cells of epithelial origin. Therefore, we hypothesize that the combination of EGFR and KRAS G12C inhibition will improve the efficacy of LY3499446 in *KRAS* G12C mutant cancers. Indeed, in vitro combination of LY3499446 and EGFR small molecule inhibitor, such as erlotinib, showed synergistic or additive effects on inhibition of cell proliferation in a panel of tumor cells with KRAS *G12C* mutation based on IC_{50} and combination index results. In a patient-derived xenograft model of lung cancer, the combination of LY3499446 with erlotinib or afatinib showed better activity than any monotherapy, and robust antitumor regression activity. Mechanistically, combining an EGFR inhibitor with LY3499446 increases KRAS G12C target occupancy and enhances inhibition of active KRAS GTP activity.

Cetuximab is an anti-EGFR monoclonal antibody that is approved for the treatment of patients with head and neck cancer and in patients with extended *RAS* wild-type CRC (Price and Cohen 2012; Goldberg et al. 2018). Activating mutations in *KRAS* and *BRAF* is well-established to have implications on therapy (Larki et al. 2017). Targeting the RAS/RAF pathway in patients with CRC has demonstrated significant challenges. While *BRAF* V600E is well-established as a prognostic marker (associated with worse median OS), it is often associated with the lack of response to cetuximab. Additionally, a decade of preclinical and clinical work has demonstrated a lack of efficacy of a single-agent BRAF inhibitor (Kopetz et al. 2015). An emergent compensatory mechanism via EGFR receptor signaling can overcome BRAF inhibition (Prahallad et al. 2012), and improved responses are seen when cetuximab is added to vemurafenib and irinotecan (Kopetz et al. 2017). More recently, the combination of encorafenib, binimetinib, and cetuximab has demonstrated improved ORR, PFS, and OS over standard-of-care (Kopetz et al. 2019).

Limitations in clinical response observed in *KRAS* G12C CRC patients treated with AMG510 is in line with other data pointing to the complex challenge of inhibiting the MAPK pathway when activating mutations are present. These challenges likely include the compensatory mechanism mediated by EGFR and the, to some extent related, control of the equilibrium between GTP/GDP-bound KRAS. Our preclinical data suggest that combining EGFR inhibitors including cetuximab with LY3499446 increases KRAS G12C target occupancy and enhances inhibition of active KRAS GTP activity. In a panel of *KRAS* G12C mutant cell lines consisting of lung, pancreatic, colorectal, esophageal, and bladder cancer cells, in vitro combination of LY3499446 and cetuximab showed synergistic or additive effects on inhibition of cell proliferation based on IC_{50} and combination index results. In 2 xenograft models of CRC, LY3499446 monotherapy demonstrated significant antitumor growth activity. However, the combination of LY3499446 and cetuximab showed more robust antitumor growth regression in both models, suggesting potential benefit of LY3499446 and cetuximab combination for CRC. Additionally, LY3499446 and cetuximab combination improved target occupancy and inhibition of active RAS activity in a CRC xenograft model.

2.3. Benefit/Risk Assessment

LY3499446 is a potent inhibitor of KRAS G12C and has demonstrated significant activity in preclinical models against a wide range of *KRAS* G12C mutant tumors. Using LY3499446 in patients with *KRAS* G12C mutations is expected to provide clinical benefit in these patients, which generally show worse OS and increased resistance to treatments compared to *KRAS* wild-type tumors and have limited treatment options.

CCI

[redacted]

. Based on the observed PK profile and the higher than anticipated exposure, the revised plan for dosing and schedule, coupled with

additional PK sampling and closer monitoring for CBC, appears to be an acceptable risk/benefit strategy.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3499446 are to be found in the Investigator's Brochure (IB).

Abemaciclib is FDA approved for the treatment of women with advanced breast cancer. Erlotinib has been commonly used in the treatment of patients with NSCLC. The use of LY3499446 with each of these combination therapies is predicted to show promising efficacy based on preclinical data reviewed in detail and available on file. The AE profiles of abemaciclib and erlotinib are well-documented and predictable.

Cetuximab is commonly used for the treatment of extended *RAS* wild-type CRC. Our preclinical data suggest that combining cetuximab with LY3499446 increases KRAS G12C target occupancy with predicted improved efficacy.

Combination with Erlotinib

Erlotinib has been associated with diarrhea, interstitial lung disease, rash, and risk of hepatotoxicity, especially in the light of underlying liver disease. LY3499446 in nonclinical studies has associated with renal and hepatic injury. There is a risk of overlapping toxicity, especially in regard to hepatic injury, and therefore, close monitoring of liver function tests will be performed through the first cycle and later on, during the study. If signs of increased liver enzymes or liver injury are observed, recommendations for monitoring and dose modifications for LY3499446 should be followed as outlined in Section 6.6.1. Monitoring and dose modifications for erlotinib should follow those provided in the product label or institutional guidelines.

Combination with Cetuximab

Cetuximab has been associated with diarrhea, interstitial lung disease, rash, hypomagnesemia, and serious infusion reactions. Sudden death has occurred in 2% of patients with head and neck cancer receiving cetuximab with radiation and in 3% of patients receiving cetuximab in combination with platinum-based therapy. While the exact risks of overlapping toxicity with cetuximab and LY3499446 remain unknown, nonclinical toxicity studies of monotherapy LY3499446 refer to hyperphosphatemia, and potential for secondary hypomagnesemia as an overlapping toxicity. Therefore, the phosphorus and magnesium levels will be monitored closely and replaced appropriately during the study. Recommendations for monitoring and dose modifications for LY3499446 should be followed as outlined in Section 6.6.1. Monitoring and dose modifications for cetuximab should follow those provided in the product label or institutional guidelines.

Combination with Abemaciclib

Abemaciclib is associated with diarrhea, fatigue, neutropenia, hepatotoxicity, and interstitial lung disease. While the exact risk of overlapping toxicity with abemaciclib and LY3499446 remains unknown, nonclinical toxicity studies suggest hepatotoxicity and possible effects on the kidney. Patients will be monitored with weekly visits and comprehensive metabolic panel weekly for the first 4 weeks and every 3 weeks or as clinically indicated thereafter. If signs of increased liver enzymes/kidney injury, or increased serum creatinine/kidney injury is observed,

recommendations for monitoring and dose modifications for LY3499446 should be followed as outlined in Section 6.6.1. Monitoring and dose modifications for abemaciclib should follow those provided in the product label or institutional guidelines.

Given the potential therapeutic benefit anticipated for LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab, the known risk profile of these combination therapies, and the benefit/risk assessment of LY3499446 monotherapy, the combination in the proposed study is considered acceptable.

More detailed information about the known and expected benefits and risks of cetuximab, erlotinib, and abemaciclib may be found in the following: Patient Information Leaflet, Package Insert, and Summary of Product Characteristics.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
Phase 1 Dose Escalation: • To characterize the RP2D for LY3499446 when administered alone or in combination with either abemaciclib, cetuximab, or erlotinib.	• DLTs • Assessment of safety including, but not limited to, TEAEs, SAEs, deaths, and clinical lab abnormalities per CTCAE v5.0
Phase 2: • To assess the efficacy of LY3499446 alone or in combination with abemaciclib or erlotinib vs. docetaxel in patients with advanced *KRAS* G12C-mutant NSCLC. • To evaluate the efficacy of LY3499446 alone or in combination with cetuximab in patients with advanced *KRAS* G12C mutant CRC. • To evaluate the efficacy of single-agent LY3499446 in patients with advanced *KRAS* G12C mutant solid tumors (other than NSCLC and CRC).	• Per RECIST v1.1: ○ ORR (primary for CRC cohorts and Other tumors cohort; coprimary for NSCLC cohorts) ○ PFS (coprimary for NSCLC cohorts)
Secondary	
Phase 1 Dose Escalation: • To characterize the safety and toxicity profile of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib (NSCLC), or cetuximab (CRC) to patients with advanced solid tumors with *KRAS* G12C mutation. • To assess the PK of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation. • To assess any antitumor activity of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation.	• Safety as determined by (including but not limited to) TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0) • Plasma concentration of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab • Per RECIST v1.1: ORR, PFS, DoR, DCR

Objectives	Endpoints
Phase 2: • To assess the efficacy of LY3499446 administered as monotherapy or in combination with abemaciclib or erlotinib in patients with NSCLC tumors harboring *KRAS* G12C mutations, and of LY3499446 administered as monotherapy or in combination with cetuximab in patients with CRC tumors harboring *KRAS* G12C mutations, and LY3499446 administered as monotherapy in patients with solid tumors, other than NSCLC and CRC, harboring *KRAS* G12C mutation. • To characterize the safety and toxicity profile of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab to patients with advanced solid tumors with *KRAS* G12C mutation. • To assess the PK of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab in patients with advanced solid tumors with *KRAS* G12C mutation.	• Per RECIST v1.1: o DoR, DCR, TTR, OS (all cohorts) o PFS (CRC cohorts and Other tumors) • Safety as determined by (including but not limited to) TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE (Version 5.0) • Plasma concentration of LY3499446 administered as monotherapy and in combination with abemaciclib, erlotinib, or cetuximab
Tertiary/Exploratory	
• To explore the association between biomarkers and clinical outcomes.	• Results of biomarker assessments and clinical outcomes

Abbreviations: CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; NSCLC = nonsmall cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time to response.

4. Study Design

4.1. Overall Design

Study JZKA is a first in human, multicenter, open-label dose escalation Phase 1 study, followed by cohort- and disease-specific randomized Phase 2.

The Phase 1 portion will enroll patients with *KRAS* G12C mutant solid tumors, where patients will be treated with monotherapy LY3499446 or LY3499446 in combination with abemaciclib, erlotinib, or cetuximab.

Once a recommended phase 2 dose (RP2D) for monotherapy and dosing in combination has been established, patients with *KRAS* G12C mutant NSCLC will be randomized across 4 cohorts, including docetaxel as an active comparator arm, to evaluate the efficacy and safety of LY3499446 alone and in combination. Depending on the relative benefit/risk assessment of different treatment regimens and the level of clinical efficacy seen, efforts will be pursued with intent to support a marketing authorization application of the optimal regimen with docetaxel as the comparator. Such efforts may include, as appropriate and upon prior consultation with the competent regulatory authorities, expanding enrollment to support a marketing authorization application with data obtained from Study JZKA.

For patients with *KRAS* G12C mutant CRC, patients will be randomized to either LY3499446 alone or in combination with cetuximab during the Phase 2 part. The purpose of this part of the study is activity estimation and continued assessment of safety.

For patients with *KRAS* G12C mutant solid tumors (other than NSCLC or CRC), an expansion cohort of LY3499446 given alone is intended to assess the potential for efficacy and to further evaluate safety. The primary purpose of this portion of the study is signal-finding in indications other than NSCLC and CRC.

Section 1.2 illustrates the study schema.

4.1.1. Phase 1

Phase 1 (dose escalation) will assess the safety and tolerability of LY3499446 to identify a monotherapy RP2D and the RP2D for each combination (abemaciclib, cetuximab, and erlotinib) in patients with advanced solid tumors with a *KRAS* G12C mutation.

Patients enrolled in Phase 1 will receive one of the following treatments:

- LY3499446 monotherapy (Cohorts A0, A1, A2, and A-1)
- LY3499446 in combination with abemaciclib (Cohorts B0, B1, B2, B3, and B-1)
- LY3499446 in combination with cetuximab (Cohorts C0, C1, C2, C3, and C-1)
- LY3499446 in combination with erlotinib (Cohorts D0, D1, D2, D3, and D-1)

The $RP2D_M$ will be determined based on the aggregate analysis of the number of observed DLTs, PK, safety, and clinical response data and may fall below the maximum tolerated dose [MTD].

Treatment cycles will consist of 21 days. A 21-day DLT observation period will apply to all cohorts in Phase 1. Refer to Section 4.1.1.1 for additional details on the dose escalation method.

In the Combination Dose Escalation cohorts (Parts B, C, and D), multiple DLs of LY3499446 will initially be explored for each combination based on the final range of dose levels evaluated and deemed safe in the monotherapy dose escalation. Initially, previously registered doses of abemaciclib, erlotinib, and cetuximab will be utilized. However, lower doses may be explored as warranted based on emerging safety data. Refer to Section 4.1.1.1 for details on the dose escalation method.

Eli Lilly and Company (Lilly) and the investigators will hold a meeting to review safety and available PK results after completion of the DLT period for each cohort to ensure it is safe to proceed with the next cohort, and determine the next dose level, and schedule. Adverse events from non-evaluable patients will also be reviewed throughout the dose escalation process in Phase 1.

In the dose escalation of LY3499446 monotherapy and the combination regimens, once a given DL is cleared for initial DLT evaluation, and if the PK supports therapeutic index, more patients could be enrolled (i.e., backfilled) to that DL while a higher DL is being evaluated for DLT. Approximately10 backfill patients may be enrolled for each cohort in Part A. Likewise, up to 10 backfill patients may be enrolled to each combination regimen. Those backfilled patients who meet the definition of DLT-evaluable population (see Section 4.1.1.1) will be included in making decisions on dose escalation. Dose-limiting toxicity evaluation at a higher DL could be halted, and additional patients could be enrolled to a DL that has cleared for initial DLT evaluation (i.e., stay) or to a lower DL (i.e., de-escalation), depending on the total number of DLTs observed among all DLT-evaluable patients at that DL (initial and backfilled patients). These aggregate safety data will be taken into account in defining the RP2D.

4.1.1.1. Dose Escalation Method

Dose escalation for monotherapy will utilize the modified toxicity probability interval-2 (mTPI-2) methodology (Guo et al. 2017) where a precalculated decision table (Appendix 8) will guide the dose recommendations until the MTD is determined (e.g., when all planned patients have been tested, or when no higher candidate DL can be tested). At the lowest DL1 of monotherapy and combinations, at least 2 patients will be tested in a cohort, while at subsequent higher DLs, a minimum of 3 patients will be enrolled in a DL cohort to estimate the DLT incidence rate. A given cohort will continue to enroll and follow patients until the observed DLT rate is either above or below the specified target incidence range. If the dose is de-escalated to -1 DL, the mTPI-2 rule will be followed, except no further de-escalation is allowed, and the study will be discontinued if necessary.

The monotherapy RP2D will be determined based on aggregate analysis of the number of observed DLTs, PK, safety, tolerability, and clinical response data.

Combination therapies will also be evaluated using the mTPI-2 methodology. The combination cohorts (Part B/C/D) will not open until the monotherapy $RP2D_M$ is established in Part A or until a monotherapy DL deemed safe by the safety review committee and associated with exposures predicted to be efficacious is achieved. Cohorts B0, C0, and D0 will utilize a LY3499446 dose at least 1 DL below the previously established safe monotherapy DL. If a sufficient number of patients experience DLTs at the first DL for a combination to warrant de-escalation, enrollment to the dose from the next lower monotherapy DL will be opened. If the DLT rate at the lowest

allowed level suggests further de-escalation, then further enrollment to that combination will be closed.

Like the 3+3 design, the mTPI-2 method incorporates prespecified escalation rules. However, the mTPI-2 method is based on quantitative models that incorporate uncertainty into the decision rules, thereby allowing more precise RP2D selection. If 3 or 6 patients are enrolled in a cohort, the escalation rule parallels a traditional 3+3 design. However, it allows for a flexible number of patients in a cohort. For example, with 2 DLTs per 6 patients enrolled, the mTPI-2 would recommend staying at the current dose, as analogy to 1 DLT per 3 patients enrolled in 3+3 design; therefore, it allows for more patients for a more precise estimate of the DLT rate at this DL.

Following a discussion between the Lilly clinical research physician/clinical research scientist (CRP/CRS) and the investigators, a more conservative dose selection/de-escalation may be applied to the next cohort (for instance, if PK or other data suggest that further dose increase would not be expected to yield additional benefit). For example, if the rule indicates "E" to escalate, the dose may stay at the current DL, be de-escalated to a lower level, or escalation may cease. In the mTPI-2, the cohort size is not fixed. However, each cohort, except for the cohort at the lowest DL in the Phase 1 part of this study, will contain a minimum of 3 evaluable patients, unless the escalation rules dictate that the dose should be de-escalated ("D" or "DU"). Doses can be escalated, de-escalated, and re-escalated. If the dose decision was "DU," the dose cannot be re-escalated to that level. This study is designed to identify a DL with a dose-limiting target toxicity rate of 30%. The mTPI-2 method considers an equivalence interval around the target toxicity rate. For this study, the equivalence interval is elicited to be (27%, 33%), indicating that any values between (27%, 33%) can be considered as accepted toxicity rates for MTD. The final MTD will be the dose for which the estimated toxicity rate is the closest to the target toxicity rate of 30% and less than 33%. The resulting mTPI-2 decision rules for any cohort size up to 25 and a hypothetical example for DLT determination after all patients complete DLT evaluations are provided in Appendix 8.

Safety data, in particular DLTs, will be the primary criteria for the dose escalation. In addition, if available at the time of the dose escalation decision, PK results (for example, C_{max}, area under the curve [AUC], and pharmacodynamics results) will be used as secondary/supporting data for dose escalation.

Intermittent dose levels or alternative schedules may be explored. Similarly, lower doses or alternative schedules of abemaciclib and erlotinib may be explored below the currently approved doses based on emerging safety data. The totality of data including safety, PK exposure, and the incidence of DLT may help guide evaluating alternative dosing and schedule (e.g. CCI CCI versus CCI CCI)

4.1.1.2. Dose-Limiting Toxicity Determination

A DLT is defined as any of the events according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 below if both the following criteria are met:

1. The event occurs during the DLT observation period of Cycle 1, between Days 1 and 21, and,

2. The event is clinically significant and not clearly related to disease progression or intercurrent illness

- Grade 3 nonhematological toxicity according to the NCI CTCAE version 5.0, with the exceptions listed below:
  - nausea lasting <72 hours
  - vomiting lasting <72 hours
  - diarrhea lasting <72 hours
  - constipation lasting <72 hours
  - electrolyte disturbance lasting <72 hours
  - rash not attributed to LY3499446
- Any Grade 4 nonhematologic toxicity, regardless of duration
- Any Grade 3 nausea, vomiting, diarrhea, or constipation lasting >72 hours despite adequate supportive care
- Any Grade 3 electrolyte disturbances lasting >72 hours despite conventional medical interventions. Grade 3 electrolyte disturbances that require hospitalization should be considered a DLT.
- Grade 4 hematological toxicity that persists more than 5 days
- Grade 3 thrombocytopenia associated with clinically significant bleeding and/or requiring platelet transfusion, or Grade 4 thrombocytopenia of any duration
- Grade ≥3 febrile neutropenia and/or neutropenia requiring granulocyte colony-stimulating factor (G-CSF)
- Grade ≥3 anemia requiring a blood transfusion
- Total bilirubin > 5× ULN, except for cases clearly related to biliary obstruction
- Confirmed Grade 2 or higher ILD during DLT assessment period
- Any death not clearly due to the underlying disease or extraneous causes and for any toxicity requiring permanent discontinuation of study drug(s).
- Any toxicities which require dose omissions of more than 20% of intended dose and which are deemed by the primary investigator and Lilly CRP/CRS to be dose limiting.
- Grade ≥2 hemolysis of any duration

Patients with normal or near normal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) at baseline (<1.5× upper limit of normal [ULN]):

- ALT or AST ≥8× ULN
- ALT or AST ≥3× ULN and total bilirubin (TBL) ≥2× ULN in the absence of significant cholestasis (i.e., alkaline phosphatase [ALP] >2× ULN).

Patients with elevated ALT or AST at baseline (≥1.5× ULN):

- ALT or AST ≥5× baseline[a].
- ALT or AST ≥3× baseline[a] and TBL ≥2× ULN in the absence of significant cholestasis (i.e., ALP >2× ULN).

[a] Multiples of baseline pertain to the aminotransferase (ALT or AST) which is elevated at baseline, respectively.

It should be recognized that for patients who have received prior immune therapy, including checkpoint inhibitors, there is the potential for delayed manifestation of serious immune-related adverse events (irAEs) such as colitis, hepatitis, pneumonitis, and endocrinopathies. Patients manifesting potential delayed irAEs should receive prompt evaluation and treatment.

Investigators, together with the Lilly CRP/CRS, can declare a DLT if a patient is experiencing increasing toxicity during treatment and it becomes clear that it is not going to be possible to complete the treatment without exposing the patient to excessive risk.

A DLT-equivalent is defined as an AE that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in the dose escalation phase, but that occurs any time after Cycle 1. Dose-limiting toxicity-equivalent toxicities may be considered in determining the RP2D.

4.1.2. Phase 2

In the Phase 2 portion, randomization will be implemented to determine the treatment for patients with NSCLC and CRC with *KRAS* G12C mutation.

For NSCLC cohorts, up to 160 patients in total will be enrolled and randomized at a 1:1:1:1 ratio to monotherapy (Cohort E1), in combination with abemaciclib (Cohort E2), in combination with erlotinib (Cohort E3), or docetaxel alone (active control; Cohort E4). An interim data review will be performed based on efficacy, safety, and PK data. Enrollment will continue while this analysis is being conducted. A final data review will be performed based on safety, efficacy, and PK data.

For CRC cohorts, approximately 40 patients will be enrolled initially and will be randomized at a 1:1 ratio to monotherapy (Cohort F1) or in combination with cetuximab (Cohort F2). Another 40 patients may be enrolled to one of the treatment arms (F1 or F2) based on the interim analysis results of the first 40 randomized patients. Cetuximab administration will begin on Cycle 1 Day 8 after a 1-week lead-in with LY3499446. An interim data review will be performed based on safety, efficacy, and PK data.

Approximately 40 patients with other tumor types associated with *KRAS* G12C mutation (other than NSCLC and CRC) will be enrolled to receive LY3499446 monotherapy (Cohort G). An interim analysis for safety and preliminary efficacy will be performed after the first 20 patients are enrolled into the cohort.

4.2. Scientific Rationale for Study Design

The overall rationale for the study design is described in the Introduction section under Study Rationale (Section 2.1) and in the Statistical Considerations (Section 9). Dose selection and justification details can be found in the Justification for Dose, Section 4.3.

4.3. Justification for Dose

Due to the safety signals observed in study JZKA in the PPD , a modified starting dose of CCI CCI is proposed as the next starting DL. The

primary goal of the modified starting dose is to minimize the risk of seeing AEs observed so far in the first 2 patients.

The original starting dose of CCI achieved exposures 2- to 6-fold higher than the average predicted exposure in the PPD treated with LY3499446. Pharmacokinetic data collected for both patients within the first 24 hours of cycle 1 are shown in the following table. Please note, the analysis of the PK data from the PPD so far in study JZKA is based on preliminary data with nominal times only. Actual time and date of PK samples and dosing time and dates were not available at the time of analysis. There could be potential discrepancies between the preliminary data and final data. Although high level conclusions from the data are not expected to change, interpretation of the analysis results should be done with caution.

Observed Pharmacokinetic Parameters PPD with Comparison to Model Predicted Values for The Average Patient Based on Nonclinical Data.

	Part A Cohort A1 LY3499446 CCI		Predicted PK
Parameter	PPD	PPD	PPD
CCI	PPD	PPD	PPD
CCI	PPD	PPD	PPD

Abbreviations: AUC [0-12] = area under the concentration vs. time curve from time 0 to 12 hours, Cmax = observed maximum serum concentration.
Note: Analysis of the PK data PPD is based on preliminary data with nominal times only.

Decreasing the dose to CCI is reasonably expected to result in lower plasma concentration. Lower dosing frequency will decrease the cumulative dose in a 48-hr period by 8-fold and result in lower AUC over the dosing interval.

Should the CCI be well tolerated without CCI or other dose-limiting toxicities, more frequent dosing regimens will be explored. In the event the CCI dosing also leads to CCI or other dose-limiting toxicities, lower doses and/or other dosing frequencies will be explored to ensure patient safety and sufficient target engagement for clinical benefit.

In conjunction to the modified starting dose and dosing interval, more frequent PK sampling and safety monitoring will also be implemented to ensure any potential adverse events are captured earlier and treatment adjusted accordingly. The collection of additional PK and safety data will aid in understanding the CCI to better inform future dose decisions in the study.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial globally.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if **all** of the following criteria apply:

Age

1. Participant must be ≥18 years of age at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who have histological or cytological evidence of a diagnosis of a locally advanced and/or metastatic solid tumor with an identified *KRAS* G12C mutation. For patients to be eligible for enrollment in Phase 2 Part E (NSCLC) or Part F (CRC), *KRAS* G12C mutation status must be determined by one of the following methods:
    - FoundationOne CDx
    - ThermoFisher Oncomine Dx
    - MSK -IMPACT

    a. Part A, B, C, and D Dose Escalation Phase:
        - Patients must be, in the judgement of the investigator, an appropriate candidate for experimental therapy and must have progressed through or be intolerant to all therapies known to confer clinical benefit, or have refused such a therapy
        - Patients are eligible if they have measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

    b. Phase 2 Part E (NSCLC):
        - Patients must have histological or cytologically proven recurrent/metastatic, unresectable NSCLC with *KRAS* G12C mutation
        - Patients must be negative for targetable oncogenic driver mutation or alteration, such as *EGFR*, *ALK*, *BRAF*, or *ROS*.
        - Patients are eligible if they have measurable disease per RECIST v1.1
        - The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after progressing on at least first-line immunotherapy and platinum-based treatment, intolerant to available standard therapies, or refused such a therapy

    c. Phase 2 Part F (CRC):
        - Patients must have histological or cytologically proven recurrent/metastatic, unresectable CRC with *KRAS* G12C mutation
        - Patients must be, in the judgement of the investigator, an appropriate candidate for experimental therapy and must have received at least 2 prior regimens of therapy for advanced or metastatic CRC including fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens
        - Patients are eligible if they have measurable disease per RECIST v1.1

    d. Phase 2 Part G (other tumors):

- Patients must have histological or cytologically proven recurrent/metastatic, unresectable solid tumors other than NSCLC and CRC, and with *KRAS* G12C mutation
- The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after progressing or being intolerant to all available standard therapies, or have refused such therapy.
- Patients are eligible if they have evaluable or measurable disease per RECIST v1.1

3. Phase 2 NSCLC and CRC patients (Cohorts E1, E2, E3, E4, F1, and F2) must be able and willing to undergo 2 biopsies as specified below. On-treatment biopsies are required if medically feasible. Cohort F2 and Cohort G patients are required to submit archival tissue. Sites should confirm availability of archival tissue with pathological laboratory prior to randomization.
    a. Patients to be enrolled into Phase 1 are not required to provide tissue (archival or new biopsy)
    b. Patients to be enrolled into Phase 2 Cohort G will be required to submit an archival tissue sample to enroll (block or freshly cut slides). If there is insufficient tissue for enrollment, a new biopsy will be required
    c. Patients to be enrolled into Phase 2 Cohorts E1, E2, E3, E4, and F1 must be able and willing to undergo pretreatment and on-treatment biopsies
    d. Patients to be enrolled into Phase 2 Cohort F2 will be required to submit an archival tissue sample to enroll (block or freshly cut slides). In addition, patients must be willing to undergo 2 on-treatment biopsies
4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale (Oken et al. 1982).
5. Have adequate organ function prior to enrollment (Phase 1) or randomization (Phase 2), as defined in the table below:

System	Laboratory Value
Hematologic	
ANC	$\geq 1.5 \times 10^9$/L
Platelets	$\geq 100 \times 10^9$/L
Hemoglobin	≥8 g/dL
Note: transfusions to increase a patient's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 14 days prior to enrollment (Phase 1) or randomization (Phase 2). If a patient receives transfusions, erythropoietin, or G-CSF therapy ≥14 days prior to enrollment (Phase 1) or randomization (Phase 2), the hematologic criteria listed above must be met following the 14-day window and prior to enrollment (Phase 1) or randomization (Phase 2).	
Hepatic	
TBL	≤1.5× ULN, patients with Gilbert's syndrome with a TBL ≤3.0 times ULN and direct bilirubin within normal limits are permitted.

System	Laboratory Value
ALT and AST	≤2.5× ULN **OR** ≤5× ULN if the liver has tumor involvement.
Renal	
Serum creatinine **OR**	<1.5× ULN **OR**
Measured creatinine clearance **OR**	≥50 mL/min/1.73 m^2
Calculated creatinine clearance (See Appendix 7)	
Coagulation	
International normalized ratio OR Prothrombin time OR Activated partial thromboplastin time	≤1.5× ULN unless participant is receiving anticoagulant therapy as long as prothrombin time or activated partial thromboplastin time is within therapeutic range of intended use of anticoagulants.

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; G-CSF = granulocyte colony-stimulating factor; TBL = total bilirubin; ULN = upper limit of normal.

6. Have discontinued all previous treatments for cancer with resolution of any AEs, with the exception of alopecia, and of all clinically significant toxic effects of prior locoregional therapy, surgery, radiotherapy, or systemic anticancer therapy to Grade ≤1. Participants must have discontinued from previous treatments, as shown in the table below:

Previous Treatment	Length of Time Prior to Enrollment (Phase 1) or Randomization (Phase 2)
Cytotoxic therapies or targeted agents that are small molecule inhibitors	≥21 days or ≥5 half-lives, whichever is shorter
Biologic agents that are large molecules including immunotherapy	≥28 days
Investigational agents	≥28 days. If the agent has a long half-life (e.g., >2 weeks), then 3 months or 5 half-lives (whichever is longer) should have passed
Radiotherapy	
Limited-field radiotherapy with palliative intent	≥14 days
Other radiotherapy	≥28 days
Major surgery, excluding biopsy	≥28 days

7. Must be able to swallow capsules.
8. Agree and adhere to contraceptive use by men or women that is consistent with local regulations regarding the methods of contraception for those participating in clinical studies. See Appendix 3 for guidance on contraceptive use and collection of pregnancy information.

9. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test documented within 7 days prior to enrollment (Phase 1) or randomization (Phase 2) (see Appendix 3).
10. Have an estimated life expectancy of ≥12 weeks.
11. Patients are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

Informed Consent

12. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

Participants are excluded from the study if **any** of the following criteria apply:

Medical Conditions

13. Disease suitable for local therapy administered with curative intent.
14. Have an active fungal, bacterial, and/or active untreated viral infection, including HIV or viral (A, B, or C) hepatitis (screening is not required).
15. The patient has a serious pre-existing medical condition(s) that, in the judgment of the investigator, would preclude participation in this study, including interstitial lung disease (ILD), severe dyspnea at rest, or requiring oxygen therapy.
16. Have a serious cardiac condition, such as:
    a. congestive heart failure
    b. New York Heart Association Class III/IV heart disease
    c. unstable angina pectoris
    d. myocardial infarction or cardiovascular event within the last 3 months before enrollment (Phase 1) or randomization (Phase 2)
    e. valvulopathy that is severe, moderate, or deemed clinically significant
    f. arrhythmias that are symptomatic or require treatment (not including patients with rate-controlled supraventricular tachycardia)
    g. have a mean QT interval corrected for heart rate of ≥470 msec on screening electrocardiogram (ECG) as calculated using Fridericia's formula (QTcF) at several consecutive days of assessment
    h. a history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of Long QT syndrome).
    i. require the use of concomitant medications that prolong the QT/QTc interval
17. Have a second active primary malignancy prior to enrollment (Phase 1), or diagnosed and/or treated for an additional malignancy within 3 years prior to randomization (Phase 2) with the exception of curatively-treated basal cell carcinoma of the skin, nonmetastatic prostate cancer treated with observation only, squamous cell carcinoma of the skin, and/or curatively resected in situ cervical and/or breast cancers.

18. Have known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously-treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without requirement of steroid treatment for at least 14 days prior to enrollment (Phase 1) or randomization (Phase 2).
19. Have prior history of hemolytic anemia

Prior/Concomitant Therapy

20. NSCLC patient otherwise eligible for enrollment in Phase 2 Cohorts E1-E4 that have received any prior LY3499446, docetaxel, EGFR inhibitors, or CDK4/6 inhibitors for systemic treatment in the Phase 2 randomized portion of the study. However, such therapy is allowed for the combination dose escalation in Phase 1 Cohorts B, C, and D.
21. Have received prior treatment with any KRAS G12C small molecule inhibitor.

Prior/Concurrent Clinical Study Experience

22. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
23. Have participated, within the last 30 days; (3 months for studies conducted in the United Kingdom [UK]), in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (3 months for studies conducted in the UK), whichever is longer, should have passed. Exceptions will be considered on a case-by -case basis by the Lilly CRP/CRS.

Other Exclusions

24. Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 180 days after the last dose of study medication.
25. Known allergic reaction against any of the components of the study treatments.

Additional Exclusion for Phase 2 Part E:

27. Patients enrolling into Phase 2 Part E (NSCLC cohorts) will be excluded if:
    a. bilirubin > ULN, or
    b. AST and/or ALT >1.5 × ULN concomitant with alkaline phosphatase >2.5 × ULN

5.3. Lifestyle Considerations

25. Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to the effect on cytochrome P450 (CYP)3A4.
26. Patients will not be permitted to use herbal supplements in any form while on study due to the unknown (UN) risk of potential drug-drug interaction.

5.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Individuals may be rescreened up to 2 times if the reason for screen failure is anticipated to have been resolved. The interval between rescreening should be ≥2 weeks. Each time rescreening is performed, the individual and/or the individual's legally acceptable representative, parent(s), or legal guardian (when applicable) must sign a new form (ICF) and will be assigned a new identification number. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

Study intervention is defined as any investigational intervention(s) or marketed product(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

The table below shows the treatment regimens for Phases 1 and 2. Doses will be administered at approximately the same times on each day. Treatment will be administered in 21-day cycles for all 3 study drugs.

Phase 1

	Study Drug(s) (Route of Administration)	Cohort	*Proposed* Doses	Dose Schedule
Monotherapy/ Part A	LY3499446 (PO)	A0[a]	CCI	QOD
		A1[b]	CCI	QD
		A2	CCI	BID
		A-1[c]	CCI	QD
Combination/ Part B/C/D	LY3499446 (PO)	B0/C0/D0	TBD	TBD
		B1/C1/D1	TBD	TBD
		B2/C2/D2	TBD	TBD
		B3/C3/D3	TBD	TBD
		B-1/C-1/D-1	TBD	TBD
	Abemaciclib (PO)	B0/B1/B2/B3	150 mg	BID
		B-1	100 mg	BID
	Cetuximab (IV)	C0/C1/C2/C3	400 mg/m^2 C1D1; 250 mg/m^2	QW
		C-1	400 mg/m^2 C1D1; 250 mg/m^2	QW
	Erlotinib (PO)	D0/D1/D2/D3	150 mg	QD
		D-1	100 mg	QD

Abbreviations: BID = twice daily; IV = intravenously; PO = orally; QD = once daily; QOD = once every other day; TBD = to be determined.

[a] In the event the CCI dosing also leads to CCI or other dose-limiting toxicities, lower doses and other dosing frequencies may be explored to ensure patient safety and sufficient target engagement for clinical benefit. These may include, for example, dose level A-1 of CCI or CCI

[b] In the event the CCI dosing should lead to CCI or other dose-limiting toxicities, a dose of CCI may be explored to ensure patient safety and sufficient target engagement for clinical benefit. As warranted by data, an intermediate dose of CCI may be explored.

[c] In the event the CCI dose should lead to CCI or other dose-limiting toxicities, a dose of CCI may be explored to ensure patient safety and sufficient target engagement for clinical benefit.

Phase 2

	Study Drug(s) (Route of Administration)	Cohort	*Proposed* Doses	Dose Schedule
Monotherapy	LY3499446 (PO)	E1/F1/G	$RP2D_M$	TBD
Combination with Abemaciclib	LY3499446 (PO)	E2	$RP2D_A$	TBD
	Abemaciclib (PO)	E2	150 mg	BID
Combination with Erlotinib	LY3499446 (PO)	E3	$RP2D_E$	TBD
	Erlotinib (PO)	E3	150mg	QD
Combination with Cetuximab	LY3499446 (PO)	F2	$RP2D_C$	TBD
	Cetuximab (IV)	F2	400 mg/m^2 C1D1; 250 mg/m^2	QW
Active Comparator	Docetaxel (IV)	E4	75 mg/m^2	Q3W

Abbreviations: BID = twice daily; DL = dose level; IV = intravenous; PO = orally; QD = daily; QW = every week; Q3W = every 3 weeks; $RP2D_A$ = abemaciclib recommended phase 2 dose; $RP2D_C$ = cetuximab recommended phase 2 dose; $RP2D_E$ = erlotinib recommended phase 2 dose; $RP2D_M$ = monotherapy recommended phase 2 dose.

Note: lower doses or alternative schedules of abemaciclib and erlotinib may be explored below the currently approved doses based on emerging safety data.

In addition to the LY3499446 dose levels specified in this section, intermittent dose levels, or alternative schedules may be explored. Similarly, lower doses or alternative schedules of abemaciclib and erlotinib may be explored below the currently approved doses based on emerging safety data. The totality of data including safety, tolerability, exposure, and the incidence of DLT may require evaluation of alternative doses and/or schedule (e.g. CCI CCI versus CCI).

Enrolled patients will receive LY3499446 administered PO with a dose and schedule based on the cohort they are enrolled in the above table. Missed doses of LY3499446 may be taken within 30 minutes on days when PK samples are scheduled, or within 2 hours on other days. Vomited

doses of LY3499446 should not be redosed. Dosing of LY3499446 should occur at least 1 hour prior to food intake or at least 2 hours after. Patients enrolled in combination cohorts will also receive abemaciclib, erlotinib, or cetuximab. Abemaciclib will be administered 150 mg BID PO on Days 1 to 21 of a 21-day cycle. Erlotinib will be administered 150 mg PO QD on Days 1 to 21 of a 21-day cycle. Dosing of abemaciclib and erlotinib with respect to food intake should follow instructions given on the respective approved label. Depending on the totality of safety, tolerability, PK, and DLT seen in the combination cohorts, lower doses of erlotinib, abemaciclib, or cetuximab may be explored. Docetaxel will be given by intravenous (IV) 75 mg/m^2 on Day 1 of every 21-day cycle.

In Cycle 1, patients enrolled into cetuximab combination cohorts will receive a loading dose of 400 mg/m^2 cetuximab as an approximately 120-minute infusion on Day 1 and then 250 mg/m^2 as an approximate 60-minute infusion on Day 8 and15 of a 21-day cycle. In Cycle 2 and beyond, patients will receive 250 mg/m^2 cetuximab as an approximately 60-minute infusion on Days 1, 8, and 15 of a 21-day cycle. Cetuximab should be administered following institutional-approved standard-of-care premedication. All concomitant medications, including premedication, should be recorded on the case report form (CRF). Close monitoring is required during the infusion, particularly during the first infusion, and for at least 1 hour after the end of the infusion. Refer to the Package Insert for further details.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drug(s) and the planned duration of each individual's treatment to the patient and study site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- at the end of the study, returning all unused medications to Lilly, or its designee, unless Lilly and sites have agreed all unused medications are to be destroyed by the site, as allowed by local law

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

5. Investigators should consult the study drug information provided in the Pharmacy Manual or label for the specific administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a Phase 1, open-label, dose escalation study followed by a randomized Phase 2 study. The Phase 2 part will implement a randomization design to mitigate the selection bias in allocating patients with NSCLC or CRC to either monotherapy or combination therapies.

Patients enrolled into the Phase 2 NSCLC and CRC cohorts will be stratified by the following factors:

- NSCLC patients
  - Lung only metastases versus others
  - Co-occurring mutations *KRAS* G12C + P53 (KP) versus *KRAS* G12C + KEAP1 or *KRAS* G12C + LKB1 (KL) versus others (K)
- CRC patients
  - Sidedness of the tumor (right versus left)
  - Sites of metastases (1 versus 2 versus >2)

6.4. Study Intervention Compliance

Patient compliance with study intervention will be assessed at each visit. A patient diary will be given to the patient in order to help patient compliance with LY3499446, recording food intake time relative to LY3499446 administration, and discussion with investigators about tolerability. Compliance will be assessed by direct questioning, counting returned capsules/tablets, and reviewing patient diaries. Patient diary evaluations will occur only in the first 2 cycles. Patients must receive 80% of assigned doses to be considered compliant with study.

Study intervention that is administered by IV will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is assured. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies, coadministration of clarithromycin, a strong CYP3A inhibitor, increased

exposure (AUC) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE) and coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF). Therefore, grapefruit or grapefruit juice as well as inducers and strong or moderate inhibitors of CYP3A should be substituted or avoided if possible (see Appendix 6). The information in Appendix 6 is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Abemaciclib and/or its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer resistance protein and renal transporters organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE1) and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such as metformin and those with a narrow therapeutic index such as digoxin and dofetilide should be substituted or avoided if possible.

Erlotinib and docetaxel are also metabolized by CYP3A4; therefore, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Appendix 6). Additionally, erlotinib is also metabolized by CYP1A2. Use of combined CYP3A4 and CYP1A2 inhibitors (eg, ciprofloxacin), cigarette smoking (CYP1A2 inducer), and concomitant use with moderate CYP1A2 inducers (eg, teriflunomide, rifampin, or phenytoin) should be avoided. For additional instructions, please refer to the approved label for erlotinib. Use of a drug that is listed in Appendix 6 when there is no appropriate clinical substitute for that drug will not be considered a protocol violation. After the DLT assessment period, close monitoring for toxicity and a dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Investigators are advised to avoid or to use caution in the use of sensitive or moderately sensitive substrates of CYP2C9 and CYP2C19 with LY3499446 (refer to Appendix 9).

The Lilly CRP/CRS should be contacted if there are any questions regarding concomitant or prior therapy. No other chemotherapy, immunotherapy, herbal supplements and/or herbal drugs intended to treat cancer, or experimental drugs will be permitted while the patients are on this study.

6.5.1. Use of Gastric pH Modifying Agents

Patients receiving erlotinib in combination with LY3499446 should administer H_2-receptor antagonists and antacids according to the approved label for erlotinib.

6.5.2. Palliative Medicine and Supportive Care

Palliative radiation therapy is permitted after discussion with and agreement of the Lilly CRP or designee for irradiating small areas of painful metastases that cannot be managed adequately using systemic or local analgesics. Such areas must not be an identified target lesion and must not constitute progressive disease (PD) or meet RECIST criteria for PD. Any symptomatic deterioration or clinical disease progression requiring, in the opinion of the investigator, other forms of specific antitumor systemic therapy will be cause for discontinuation of study therapy.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the CRF. Replacement hormonal therapy initiated before study entry will be allowed.

Patients should receive full supportive care. Hematopoietic growth factors (e.g., erythropoietin or G-CSFs) may be administered according to institutional guidelines and the local Package Insert, except in the DLT observation period. Hematopoietic growth factors will be allowed in the DLT observation period if a patient experiences neutropenia that is declared an AE. Administration of G-CSFs prior to first occurrence of neutropenia is prohibited. Blood product transfusions are permitted throughout the study. If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to American Society of Clinical Oncology (ASCO) guidelines (Rizzo et al. 2008). Prophylactic antibiotic treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

All concomitant medications should be recorded throughout the patient's participation in the study.

6.5.3. Supportive Management for Diarrhea

Participants should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the participant should initiate antidiarrheal therapy (for example, loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Participants should also be encouraged to drink fluids (that is, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess the response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to at least Grade 1 (per CTCAE Version 5.0), dosing of LY3499446 and, as applicable, abemaciclib, cetuximab, or erlotinib should both be suspended until diarrhea is resolved to at least Grade 1.
- When treatment recommences, dosing should be adjusted as outlined in Section 6.6.1. For severe cases of diarrhea, the measurement of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered. If diarrhea is severe (requiring IV hydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones should be considered and treatment should be suspended and appropriate dose modification should be instituted per protocol.

Participants with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluids and electrolyte replacement as clinically indicated. Please refer to Section 6.6 for specific dose-related modifications for diarrhea.

6.6. Dose Modification

The sections below detail dose modification and delays of LY3499446, abemaciclib, cetuximab, erlotinib, and docetaxel. If any study drugs are permanently discontinued, dosing could be continued with the remaining compound(s) according to the schedule, if clinically indicated. Treatment cycles may be delayed up to 7 days due to holidays, weekends, bad weather, or other unforeseen circumstances, and will not be deemed as protocol violation.

When a study drug is delayed, if possible and appropriate, patients should resume study treatment within 1 treatment cycle and, if not possible, then every effort should be made to start on the first day of the next dosing cycle. In rare circumstances, a delay >21 days may be permitted before permanent treatment discontinuation, as long as the patient has clinical benefit without objective disease progression and is recovering from the toxicity. Such circumstances must be discussed with the Lilly CRP/CRS. All dose modifications should be documented, including the approach taken and a clear rationale for the need for modification. Dose reductions will not be permitted during the DLT period.

Any patient who requires a dose reduction will continue to receive the reduced dose for the remainder of the study.

6.6.1. Dose Modification of LY3499446

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 DL – investigator's discretion.
Hematologic toxicity	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 DL.
Hematologic toxicity	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 DL. If at lowest DL, then discontinue from study.
Hematologic toxicity: **Patient requires administration of blood cell growth factors**	Regardless of severity. (growth factors use according to ASCO guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 DL unless already performed for incidence of toxicity that led to the use of growth factor. If at lowest DL, then discontinue from study.
Nonhematologic toxicity (except diarrhea and alopecia)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MAY** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MAY** be reduced by 1 DL – investigator's discretion.
Nonhematologic toxicity (except alopecia)	Grade 3 or 4 that does not resolve with maximal supportive	Dose **MUST** be suspended until toxicity resolves to	Dose **MUST** be reduced by 1 DL.

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
	measures within 72 hours to baseline or Grade 1	either baseline or Grade 1.	
Hepatic toxicity	Grade 3	Dose **MUST** be suspended	Dose **MUST** be reduced by 1 DL after toxicity returns to Grade ≤1
	Grade 4	Dose **MUST** be suspended.	Patient **MUST** be discontinued from study.
Diarrhea	Requires hospitalization for Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 DL for any Grade 4 and for Grade 3 diarrhea lasting > 3 days despite maximum supportive care
Diarrhea	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 DL – investigator's discretion.
Diarrhea	Persistent or recurrent Grade 1 that does not resolve with maximal supportive measures within 24 hours to baseline	Patient to be followed for 48 hours to ensure grade does not worsen.	Dose **MAY** be maintained during monitoring – investigator's discretion.
Diarrhea	Grade ≥2 diarrhea recurs despite maximal supportive measures after resuming same DL after initial Grade 2 diarrhea	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 DL.
Bloody diarrhea	Any grade	Dose **MUST** be suspended until bloody diarrhea resolves and diarrhea resolves to at least Grade 1.	Dose **MUST** be reduced by 1 DL.
QTcF Prolongation	≤ Grade 2 (QTcF average of triplicate readings >480 ms but ≤500 ms)	Continue at current dose level.	

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
	Grade 3 (QTcF average of triplicate readings >500 ms)	Withhold treatment; if QTcF returns to within 30 ms of baseline or <450 ms within 14 days, treatment may be resumed at a reduced dose. If the event recurs a second time, treatment will be terminated.	
	Grade 4 (QTcF average of triplicate readings >500 ms or >60 ms change from baseline and TdP or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Treatment should be terminated.	
Interstitial Lung Disease	Grade 1	Continue to monitor without dose modification.	
Confirmed Interstitial Lung Disease	Grade 2 to 4	Discontinue and institute appropriate therapy.	

Abbreviations: ASCO = American Society of Clinical Oncology; DL = dose level.

The table below provides additional guidance for responding to treatment-emergent adverse events suggestive of hemolysis:

Treatment-Emergent Adverse Event	Action
Hemoglobin decrease of ≥2 grams/dL OR Elevated total bilirubin, ≥ Grade 2 OR Indirect bilirubin ≥ upper limit of normal	Obtain hemolysis workup including: 1. Peripheral blood smear 2. Haptoglobin 3. LDH 4. Reticulocyte count 5. Direct Coombs 6. Indirect Coombs 7. B12, folate, iron level, ferritin, TIBC If these laboratory values suggest hemolysis, hold drug and institute every other day monitoring of hematologic parameters. Do not resume study drug without approval from the Sponsor medical monitor. Decision to resume with dose reduction or permanent discontinuation will be based on the severity of the event and dose at which it occurred, as well as consideration of any clinical benefit the patient is achieving related to study drug.

Abbreviations: LDH = lactic dehydrogenase; TIBC = total iron binding capacity.

6.6.2. Dose Modification of Abemaciclib

Dose adjustments as outlined in the following table are allowed. Abemaciclib should be reduced sequentially by 1 dose level. For patients requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP/CRS. After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient is currently receiving.

Dose Adjustments of Abemaciclib

Dose Adjustment	Oral Dose	Frequency
0	150 mg	Twice Daily with at least 6 hours between doses
1	100 mg	Twice Daily with at least 6 hours between doses
2	50 mg	Twice Daily with at least 6 hours between doses

If a patient receiving the 50-mg twice daily dose of abemaciclib requires further dose reduction, the patient must be discontinued from abemaciclib.

Abemaciclib Dose Adjustments for Treatment-Related Adverse Events

Treatment-emergent laboratory abnormalities of neutrophil count decreased and/or ALT/AST increased, regardless of clinical significance, must follow the dose adjustment table below.

Toxicity Type	Toxicity Profile and Severity	Abemaciclib Dose Suspension	Abemaciclib Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose reduction is **NOT** required.
	Recurrent[a] Grade 3 or Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity: If patient requires administration of blood cell growth factors	Regardless of severity (Use of growth factors according to ASCO guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor.

Toxicity Type	Toxicity Profile and Severity	Abemaciclib Dose Suspension	Abemaciclib Dose Reduction
Nonhematologic Toxicity[b] (except diarrhea, ALT increased, and ILD/pneumonitis, and VTE[c])	Persistent or recurrent[a] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Grade 2 that does not resolve within 24 hours to ≤Grade 1	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MAY** be reduced by 1 dose level.
	Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Any grade that requires hospitalization	Dose **MUST** be suspended until toxicity resolves to ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5.0-20.0×ULN)[d]	Dose **MUST** be suspended until toxicity resolves to baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Grade 4 (>20.0×ULN)	Abemaciclib treatment **MUST** be discontinued	Abemaciclib treatment **MUST** be discontinued
ALT Increased with increased total bilirubin, in the absence of cholestasis	Grade 3 increased ALT (>5.0×ULN) with total bilirubin >2×ULN	Abemaciclib treatment **MUST** be discontinued.	Abemaciclib treatment **MUST** be discontinued.
ILD / pneumonitis	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to either baseline or ≤Grade 1.	Dose **MUST** be reduced by 1 dose level.
	Grade 3 or 4	Abemaciclib treatment	Abemaciclib treatment

Toxicity Type	Toxicity Profile and Severity	Abemaciclib Dose Suspension	Abemaciclib Dose Reduction
		MUST be discontinued.	**MUST** be discontinued.

Abbreviations: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; ILD = interstitial lung disease; ULN = upper limit of normal; VTE = venous thromboembolic event.

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event).

[b] Additional guidance for hepatic and renal monitoring is in Section 8.2.1.1 and Section 8.2.1.2.

[c] For VTE, dose reduction of abemaciclib will be at the discretion of the investigator.

[d] Grade 3 ALT/AST increased is a trigger for additional assessments and possibly hepatic monitoring.

If a patient receiving the 50-mg twice daily dose of abemaciclib requires further dose reduction, the patient must be discontinued from abemaciclib. Patients undergoing surgery:

- For minor surgeries and procedures (for example, ambulatory), investigators should treat as clinically indicated and closely monitor any signs of infection or healing complications.
- For major surgeries, the recommendation is to suspend dosing of abemaciclib for at least 7 days before and may be resumed as clinically indicated.
- Consider monitoring neutrophils and platelets before surgery and before resuming abemaciclib. The scars should be aseptic and healing process be reasonable before resuming abemaciclib.
- Dose suspensions ≥28 days must be discussed with Lilly CRP/CRS.

At the investigator's discretion with consultation with the Lilly CRP/CRS, patients may continue on LY3499446 if they discontinue from abemaciclib. Based upon the toxicity's relation to the study drug, the investigator may choose to reduce one or both study treatments.

6.6.3. Dose Modification of Cetuximab

Reduce, delay, or discontinue cetuximab treatment to manage adverse reactions as described in the table below:

Reaction	Severity	Dose Modification
Infusion reactions	Grade 1 or 2	Reduce infusion rate by 50%.
	Grade 3 or 4	Immediately and permanently discontinue cetuximab.

Reaction	Severity	Dose Modification
Dermatologic toxicities and infectious sequelae (eg acneiform rash, mucocutaneous disease)	First occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks. If condition improves, continue at 250 mg/m^2. If no improvement, discontinue cetuximab.
	Second occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks. If condition improves, continue at 200 mg/m^2. If no improvement, discontinue cetuximab.
	Third occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks. If condition improves, continue at 150 mg/m^2. If no improvement, discontinue cetuximab.
	Fourth occurrence; Grade 3 or 4	Discontinue cetuximab.
Pulmonary toxicity	Acute onset or worsening pulmonary symptoms	Delay infusion 1 to 2 weeks. If condition improves, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks or interstitial lung disease/pneumonitis is confirmed, discontinue cetuximab.

At the investigator's discretion with consultation with the Lilly CRP/CRS, patients may continue on LY3499446 if they discontinue from cetuximab. Based upon the toxicity's relation to the study drug, the investigator may choose to reduce one or both study treatments.

6.6.3.1. Treatment Adjustments in Case of Cetuximab Allergic/Hypersensitivity Reaction

Treatment adjustments in the event of cetuximab-caused allergic/hypersensitivity reactions should follow institutional practice. The following table is provided as guidance to investigators:

Grade	Event	Treatment
1	Transient flushing or rash; drug fever <38°C (<100.4°F)	Decrease cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 4 hours.
2	Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C (≥ 100.4°F)	Stop cetuximab infusion. Administer bronchodilators, oxygen, etc., as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 and monitor closely for any worsening.
3	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Stop cetuximab infusion immediately and disconnect infusion tubing from the patient. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Patients have to be withdrawn immediately from the treatment and must not receive any further cetuximab treatment.
4	Anaphylaxis	

Once the cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the patient has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped, and cetuximab treatment should be discontinued. If a patient experiences a Grade 3 or 4 allergic/hypersensitivity reaction at any time, cetuximab should be discontinued. If there is any question as to whether an observed reaction is an allergic/hypersensitivity reaction of Grade 1 to 4, Lilly should be contacted immediately to discuss and grade the reaction.

6.6.4. Dose Modification of Erlotinib

Dose modifications of erlotinib should follow the product label and institutional guidelines. At the investigator's discretion with consultation with the Lilly CRP/CRS, patients may continue on LY3499446 if they discontinue from erlotinib. Based upon the toxicity's relation to the study drug, the investigator may choose to reduce one or both study treatments.

6.6.5. Dose Modification of Docetaxel

Dose modifications of docetaxel should follow the product label and institutional guidelines.

6.6.6. Dose Modification for Grade 3 Toxicities Not Clearly Related to LY3499446 or Drug Given in Combination

In the event of Grade 3 toxicity in any of the combination arms, both agents should be held until toxicity has resolved or decreased to Grade 1. At the time of reinitiating therapy, 1 or both of these agents MUST be reduced by 1 DL per the investigator's discretion or after discussion with the Lilly CRP/CRS. For a specific toxicity addressed in Section 6.6.1, the investigators should reference the dose modification requirements specific to that particular toxicity.

6.7. Intervention after the End of the Study

The end of study definition is defined in Section 4.4. Investigators will continue to follow the SoA provided in Section 1.3 until notified by Lilly that end of study has occurred.

6.7.1. Treatment after Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow the SoA (Section 1.3) for all patients until notified by Lilly that study completion has occurred.

6.7.1.1. Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if at least 1 participant is still receiving study intervention when study completion occurs. Lilly will notify investigators when the continued access period begins. Lilly may allow patients to enroll in a "rollover" protocol to provide long-term continued access for patients enrolled in this study.

The continued access period will begin after study completion and ends at the end of study. The participant's continued access to study treatment will end when a criterion for discontinuation is met (Section 7). Continued access follow-up will begin when the participant and the investigator agree to discontinue study treatment. Follow-up procedures will be performed as shown in the SoA (Section 1.3).

Participants who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the short-term follow-up visit is completed. Long-term follow-up does not apply.

Participants who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Possible reasons leading to permanent discontinuation of investigational product:

- **Subject Decision**
  - the participant or the participant's designee, for example his or her parents or legal guardian, requests to discontinue investigational product.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study, and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

In addition, participants will be discontinued from the investigational product in the following circumstances:

- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment
- disease progression. Exceptions for continuing study treatment beyond confirmed radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from study treatment, and the investigator and the sponsor agree that continuing study treatment is in the patient's best interest
- unacceptable toxicity
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent
- the investigator decides that the patient should be discontinued from study treatment.

Participants discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 (SoA), Section 8.3 (AEs and SAEs), and Section 8.2 (Safety Assessments) of the protocol.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

- the patient or the patient's designee requests to be withdrawn from the study
- the patient becomes pregnant during the study. See Section 8.3 regarding regulatory reporting requirements on fetal outcome.

Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (SoA), Section 8.3 (AEs and SAEs), and Section 8.2 (Safety Assessments) of this protocol.

Participants who withdraw their consent from the study and request to discard their genetic and biomarker samples will have their samples destroyed. Analysis results that are available before the consent withdrawal may be published in articles or other disclosures without identifiable individual patient information.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment, unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled participant to continue in the study, with or without treatment with investigational product. Safety follow-up is as outlined in Section 1.3 (SoA), Section 8.3 (AEs and SAEs), and Section 8.2 (Safety Assessments) of the protocol. Refer to Appendix 5 for country-specific requirements related to the discontinuation of inadvertently enrolled patients in the UK.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented, and the participant will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

The discontinuation of specific sites or of the study as a whole is handled as part of Section 10.1.7.

8. Study Assessments and Procedures

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

8.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3).

Response Evaluation Criteria in Solid Tumors v1.1 (Eisenhauer et al. 2009) will be applied as the primary criteria for assessment of tumor response and date of disease progression. The method of tumor assessment used at baseline must be used consistently throughout the study. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging (MRI) is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast are required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses, but cannot be used to assess response according to RECIST v1.1.

Efficacy assessments include tumor evaluation every 6 weeks after treatment initiation through Week 24, and then approximately every 9 weeks thereafter. Patients who discontinue treatment

without documented progression should continue to be assessed per the above schedule until disease progression is observed or the patient starts subsequent anticancer therapy.

All patients are required to undergo chest/abdomen/pelvis and brain imaging at baseline and subsequent serial scans at disease assessment timepoints. All scans will be collected and stored at a central facility for central reviewer assessment during the study. Response will be assessed per RECIST v1.1 requirements (Eisenhauer et al. 2009).

Finally, all patients will enter long-term follow-up for confirming disease progression if not occurring on treatment, subsequent anticancer therapy(ies), and survival.

Baseline disease assessment with radiographic tumor measurements using CT or MRI of the chest, abdomen, pelvis, or any other areas with suspected disease involvement, must occur within 28 days of Cycle 1 Day 1. During Phase 2, brain imaging is required at baseline for patients with a history of CNS metastases or other patients if clinically indicated, and subsequent serial scans if brain metastases are present at baseline (MRI preferred, CT with contrast is acceptable if MRI contraindicated). For each modality, IV and oral contrast should be utilized (chest CT does not require IV contrast) unless there is a clear contraindication (e.g., decreased renal function or allergy that cannot be addressed with standard prophylactic treatments). In the absence of known or suspected disease involvement, head and neck CT/MRI scans are not required for malignancies other than those originating in the head and neck region. Other areas of scanning may also differ depending on disease type. Postbaseline scans should be performed every 6 weeks (±7 days) for 6 months and every 9 weeks (±7 days) thereafter, including imaging of the chest, abdomen, and pelvis, using the same modality(ies) as used for baseline imaging assessment until PD, withdrawal of consent, or initiation of (a) new anticancer therapy(ies). Additionally, any studies performed at baseline that are positive for sites of disease should be repeated at all postbaseline assessments. Additional studies can also be performed as clinically indicated. In addition, investigators may conduct an initial tumor evaluation on Cycle 2 Day 1 (±7 days) and a confirmatory tumor evaluation a minimum of 4 weeks (i.e., 28 days) after the first tumor evaluation that shows a complete response (CR) or partial response (PR) by RECIST v1.1 (or Response Assessment in Neuro-Oncology, as appropriate to tumor type), if consistent with local regulatory authority requirements. In addition, an initial postbaseline assessment on Cycle 2 Day 1 (±7 days) is encouraged if consistent with regulatory guidelines. If a scan is performed on Cycle 2 Day 1, the next scan should continue according to the schedule above (beginning at Cycle 3 Day 1). All scans will be collected and stored at a central facility to permit central reviewer assessment. A blinded independent data review may be considered in order to confirm response rate across the study cohorts. Please see the Site Imaging Manual for guidelines on how the various imaging studies should be performed.

Best Overall Response (BOR)

Subjects' BOR will be categorized as CR, PR, stable disease (SD), PD, or UN according to RECIST v1.1 criteria. As the phases of the study intended to provide a definitive analysis of response are randomized, CR and PR BOR status need not be confirmed. To qualify as a response other than PD or UN, a subject's BOR must be observed at least 6 weeks postbaseline. A PD observed prior to that point will qualify as the subject's BOR. Otherwise, if a subject does not have an adequate disease assessment, per RECIST v1.1 criteria, a BOR of UN will be assigned.

Overall response rate is the proportion of patients who achieved a CR or PR out of all patients treated. Tumor responses will be measured and recorded using RECIST v1.1 guidelines (Eisenhauer et al. 2009). To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the sample method that was used at baseline. Disease control rate (DCR), defined as the proportion of patients who achieved a CR, PR, or SD out of all patients treated, will also be summarized.

Disease control rate is the proportion of enrolled patients who have a BOR of confirmed CR, confirmed PR, or SD. Best response is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR.

Duration of response (DOR) is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST v1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. Duration of SD will be calculated only for patients with the best response of SD. It is measured from the date of start of treatment to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For each patient who is not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, duration of SD will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Progression-free survival will be defined as the time from study enrollment to the first observation of a PD overall response or death without documented disease progression per RECIST v1.1 criteria. Patients not known to have either of these events will be censored. A full description of censoring rules is provided in Section 9.4.3.2.

Overall Survival

Overall survival will be defined as the time from study enrollment to death from any cause. Patients alive at the end of the study, who have withdrawn from the study, or who are lost to follow-up will be censored on their last known alive date.

See Section 9.4.3 for further definitions of the efficacy endpoints.

8.2. Safety Assessments

For each patient, ECGs, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3). Results from any clinical laboratory test analyzed by a central laboratory (refer to Appendix 2) will be provided to investigative sites by Lilly or its designee.

Refer to Section 8.3 for details on the recording of AEs.

8.2.1. Electrocardiograms

On-treatment ECGs in Phase 1 will be 12-lead triplicate assessments obtained at the time points indicated in the SoA (Section 1.3). Patients must be supine for approximately 5 minutes in a quiet environment before ECG collection and remain supine but awake during ECG collection.

After enrollment, if a clinically significant increase in the QT/QTcF interval from baseline or other clinically significant change from baseline is identified, the patient will be assessed by the investigator for symptoms (e.g., palpitations, near syncope, or syncope) and to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly for storage.

8.2.2. Clinical Safety Laboratory Assessments

Lilly or its designee will provide the investigator with the results of safety laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or until the completion of Visit 801 after the last dose of study intervention should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a disease diagnosis (for example, hypertension, neutropenia, etc.), this should be reported in the CRF as an AE. Do not enter the test abnormality, enter the disease diagnosis or categorical term. If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE, or dose modification), then the event(s) must be reported in the CRF as AE(s).

8.2.2.1. Hepatic Safety Monitoring

In study participants with baseline ALT/AST<1.5× ULN:

If a study participant enrolled with baseline ALT/AST <1.5× ULN, experiences elevated ALT/AST ≥5× ULN, or elevated ALT/AST ≥3× ULN and TBL ≥2× ULN, liver testing

(Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

In study participants with baseline ALT/AST ≥1.5× ULN:

If a study participant enrolled with baseline ALT/AST ≥1.5× ULN, experiences elevated ALT/AST ≥3× baseline or ALT/AST ≥2× baseline and TBL ≥2× ULN, liver testing (Appendix 4) including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the study CRP/CRS. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

8.2.2.1.1. Special Hepatic Safety Data Collection

Additional safety data should be collected via the CRF/electronic data entry/designated data transmission methods if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT/AST <1.5× ULN:

- Elevation of serum ALT/AST to ≥5× ULN on 2 or more consecutive blood tests
- Elevated ALT/AST ≥3× ULN and elevated TBL ≥2× ULN

In participants enrolled with baseline ALT/AST ≥1.5× ULN

- Elevated ALT/AST ≥3× baseline on 2 consecutive tests
- Elevated ALT/AST ≥2× baseline and elevated TBL ≥2× ULN

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be a SAE

8.2.2.2. Guidance for Monitoring Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate (GFR). Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measurement used to assess a patient's renal function.

Dose alterations (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. Other measures of renal function such as cystatin C GFR should be used as an alternative to either creatinine or creatinine calculations of GFR since creatinine would not be an accurate method to assess renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for nonhematological toxicities if considered related to abemaciclib.

8.2.2.3. Guidance for ILD/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for abemaciclib. Additional information is available in the IB.

Investigators should ask patients to report any new or worsening respiratory symptoms, such as cough, dyspnea, or fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high resolution computed tomography, bronchoalveolar lavage, and biopsy, as clinically indicated.

Refer to Section 6.6.2 for guidance on dose adjustments of abemaciclib for patients.

8.3. Adverse Events and Serious Adverse Events

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each participant's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause-and-effect relationship among the investigational product, study device and/or study procedure, and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying, if possible, the circumstances leading to any dosage modifications or discontinuations of treatment.

Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.1) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the CRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Serious AEs, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to LY3499446.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to Lilly begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving LY3499446, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant and/or legal guardian is the preferred method to inquire about AE occurrences.

8.3.2. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the Institutional Review Board/IEC, if appropriate, according to local requirements.

8.3.4. Pregnancy

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 3.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy.

8.3.5. Cardiovascular and Death Events

Events leading to the clinical outcome of death due to study disease that are part of the efficacy analyses for this study will not be reported to Lilly or its designee as SAEs unless the investigator believes the event may have been caused by the investigational product.

8.3.6. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.4. Treatment of Overdose

Refer to the IB and/or Product Label for intervention or comparator for available information on the signs, symptoms, and treatment of overdose.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine the plasma concentrations of LY3499446, erlotinib, abemaciclib and its metabolites (LSN2839567 and LSN3106726), and serum concentrations of cetuximab.

A maximum of 5 samples, in addition to those shown in the SoA (Section 1.3), may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Blood samples will be obtained from a peripheral location and not the central line. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Blood samples will be analyzed at a laboratory approved by the sponsor. Plasma concentrations of LY3499446, erlotinib, and abemaciclib and its metabolites will be assayed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Serum concentrations of cetuximab will be assayed using a validated enzyme-linked immunosorbent assay method.

Urine samples (collected over approximately 12 hours) will be collected from all patients for determination of LY3499446 concentrations in urine on Cycle 1 Day 8. Total urine output for the 12 hours post-administration of LY3499446 will be collected, pooled, and refrigerated. Urine collection for determination of LY3499446 should cease after the 12-hour collection. For the collection period (0-12 hr), the total urine volume will be recorded, and 2 approximately 10-mL samples will be stored frozen. The remaining urine will be discarded. Instructions for the collection and handling of the urine samples will be provided by the sponsor.

Urine samples will be analyzed at a laboratory designated by the sponsor. Urine concentrations of LY3499446 will be quantified using an LC-MS/MS assay. The remaining urine samples may be used for exploratory metabolism work. Results from exploratory metabolism work will not be included in the final integrated study report.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 1 year following last participant visit for the study. During this time, blood samples remaining after the bioanalyses may be analyzed for exploratory drug metabolism work and other PK/pharmacodynamics work, as deemed appropriate by the sponsor. The results of such exploratory metabolism work may only be included in the clinical study report (CSR) if deemed appropriate by the sponsor or may be reported in a separate exploratory metabolism report.

8.6. Pharmacodynamics

Samples collected to measure pharmacodynamic biomarkers will be identified by the participant number (coded) and retained at a facility selected by Lilly or its designee for a maximum of 15 years following last participant visit for the study at a facility selected by Lilly or its designee. See section 8.8 for biomarker information.

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3499446, to investigate genetic variants thought to play a role in cancer, and to determine whether genetic alterations identified in tumor samples are somatic or germline variants. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/institutional review boards (IRBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3499446 or after LY3499446 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid, ribonucleic acid, proteins, lipids, and other cellular elements.

Serum, plasma, and tumor tissue samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to study treatment, pathways associated with study treatment, mechanism of action of study treatment, and/or research method in validating diagnostic tools or assays related to cancer. Additionally, samples may be used to confirm the tumor KRAS G12C mutation status.

Collection of the following tumor tissue sample(s) is **required** for Cohorts E1, E2, E3, E4, and F1 patients to participate in this study:

- A newly obtained baseline biopsy specimen (archival tissue will be requested if new biopsy insufficient)

- An on-treatment biopsy specimen collected at a time specified in Section 1.3 if medically feasible

Collection of the following tumor tissue sample(s) is **required** for Cohort F2 patients to participate in this study:

- Archival tumor tissue block or freshly cut slides, sites should confirm the availability of tumor tissue with the pathological laboratory prior to randomization
- Two on-treatment biopsy specimens collected at times specified in Section 1.3 if medically feasible

Collection of the following tumor tissue sample(s) is **required** for Cohort G patients to participate in this study:

- Archival tumor tissue block or freshly cut slides (new baseline biopsy required if insufficient archival tissue available), sites should confirm the availability of tumor tissue with the pathological laboratory prior to enrollment

Collection of the following tumor tissue sample(s) is **optional** for Phase 2 cohort E1, E2, E3, F1, and F2 patients participating in this study:

- New biopsy at progression for patients on treatment for at least 6 months who have had PR or CR.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3499446 or after LY3499446 becomes commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, and/or immunohistochemistry, may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

The pathology report accompanying archival tissue may also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Lilly has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.7 and 8.8. These results may not be disclosed to patients because this research is considered exploratory.

8.9. Medical Resource Utilization and Health Economics

Health Economics and Medical Resource Utilization parameters will not be evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The statistical hypothesis for the dose escalation phase of this study is that at least 1 evaluated DL for LY3499446 will have an estimated DLT rate that is within or below the target range of 27% to 33%, when administered alone or in combination with abemaciclib, erlotinib, or cetuximab.

The statistical hypothesis for the Phase 2 part of the study is that durable objective responses will occur at a rate indicative of clinically relevant activity within the selected monotherapy and combination regimens.

For NSCLC, the statistical hypothesis is LY3499446 alone or in combination with erlotinib or abemaciclib will lead to significant and clinically meaningful improvement in ORR and PFS when compared to docetaxel.

9.2. Sample Size Determination

This study will consist of 2 segments, a Phase 1 dose escalation, and a Phase 2 evaluation of clinical activity. The Phases 1 and 2 segments will each evaluate both monotherapy and combination regimens.

Phase 1 segment

The dose escalation phase will initially evaluate doses in sequentially opened cohorts, with the possibility to explore additional immediate doses or schedules. Dose escalation will implement the mTPI-2 methodology. While the mTPI-2 algorithm allows for escalation after as few as 1 patient is evaluated, a minimum of 3 evaluable patients will be enrolled in each cohort for DLT evaluations. Thus, approximately up to 25 patients will be enrolled across monotherapy regimen DLs for dose-escalation evaluations, plus 10 patients per cohort as backfills, totaling approximately 45 patients in Part A. With 4 DL cohorts, this will assure a sufficient number of patients will be dosed at the MTD to allow adequate characterization of the overall safety profile.

Combinations with abemaciclib, erlotinib, and cetuximab will be independently evaluated using the mTPI-2 methodology. Approximately 22-30 evaluable patients will be enrolled to each combination regimen (including up to 10 patients enrolled as “backfills” per cohort).

Phase 2 segment

Once an RP2D is established for all 4 regimens, enrollment to the Phase 2 portion for initial evaluation of clinical activity will begin. There will be 7 cohorts opened.

In NSCLC, the treatment arms will be (with corresponding targeted ORR):

- LY3499446 monotherapy (targeted ORR = 35%)
- LY3499446 in combination with erlotinib (targeted ORR = 55%)
- LY3499446 in combination with abemaciclib (targeted ORR = 55%)
- Docetaxel (historical ORR = 15%)

In patients with CRC, the treatment arms will be:

- LY3499446 monotherapy (targeted ORR = 15%)
- LY3499446 in combination with cetuximab (targeted ORR = 25%)

A cohort of patients with solid tumors other than NSCLC or CRC whose tumors harbor the *KRAS* G12C mutation will be treated with LY3499446 monotherapy.

An interim analysis will be conducted within each cohort once approximately 20 patients have been enrolled in each arm and evaluated for response per RECIST v1.1. Patients who do not complete an on-treatment or poststudy treatment assessment will be considered nonresponders for analysis purposes and will not be replaced. After the interim, enrollment will continue in the remaining arms until at least 20 additional patients are enrolled in each treatment arm.

With a 1-sided significance level of 0.10, we have 80% statistical power to detect a 20% difference in response rate (assuming LY3499446 monotherapy: 35% versus control: 15%) with approximately 40 patients per arm. With the same 1-sided significance level of 0.10, we have >99% statistical power to detect a 40% difference in response rate (assuming LY3499446 combination: 55% versus control: 15%) with approximately 40 patients per arm.

For the single-arm Cohort G, with a 1-sided significance level of 0.10, we have 85% statistical power to detect a response rate difference of 10%, assuming a historical control rate of 5% and a response rate of 15% under the alternative.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent
DLT evaluable	All patients enrolled in the dose escalation phase (Phase 1) who either complete 3 weeks of follow-up and at least 80% of treatment doses or discontinue treatment prior to 3 weeks due to a DLT. Patients enrolled into the cetuximab combination cohorts must receive 2 out of 3 cetuximab doses to be considered DLT evaluable.
Randomized	(Phase 2 portion only). All patients with either CRC or NSCLC who are randomized to a treatment regimen, regardless of whether they take any study drug.
PK evaluable	All enrolled patients who have at least 1 postbaseline evaluable PK sample.
Safety	All participants who take at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to their initial dose of study treatment, even if it is not the treatment to which they were assigned. In the event of a treatment error, participants will be analyzed according to the treatment they actually received. "Enrolled" population also refers to the "Safety" population in this study.
Phase 1	All patients assigned to a treatment cohort during the dose escalation (Phase 1) portion of the study.
Phase 2	All patients randomized to treatment during the Phase 2 portion of the trial (NSCLC and CRC cohorts), regardless of whether the cohort to which they are assigned is closed during or at the end of the Phase 2 portion of the study or continues to Phase 3. All patients enrolled to the "Other Tumors" cohort

	(nonrandomized).

Abbreviations: CRC = colorectal carcinoma; DLT = dose-limiting toxicity; NSCLC = nonsmall cell lung cancer; PK = pharmacokinetics.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Efficacy analyses will be conducted on the set of all enrolled (i.e., safety) patients within each phase of the study. This set includes all data from all enrolled participants within a study phase, according to the treatment the participants were assigned.

All tests of treatment effects will be conducted at a 1-sided 0.05 alpha level, as appropriate for the comparison, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

A detailed description of participant disposition will be provided at the end of the study, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as number and percentage of patients completing the study, as defined in the statistical analysis plan (SAP), or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.4.2.2. Participant Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population. A summary of baseline patient and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported using descriptive statistics.

9.4.2.3. Concomitant Therapy

A summary of prior and concomitant medications by treatment cohort will be reported.

9.4.2.4. Treatment Compliance

Study treatment compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of capsules/tablets dispensed and returned over the course of the patient's treatment. The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

Phase 1

There is no primary efficacy endpoint for the Phase 1 portion of the study, as the primary objective is to determine an RP2D, based on the incidence of DLTs and totality of data (including, but not limited to, PK, target occupancy, and clinical response data).

Phase 2

For the Phase 2 portion of the study, the primary analysis will be an evaluation of whether any of the treatment regimens are likely to provide a clinically relevant level of activity. This will be based on an evaluation of the ORR within each treatment arm, and evaluation of PFS in the NSCLC cohorts. Primary efficacy assessment will be based on an independent review of imaging data. Comparative analyses will be done for Phase 2, Cohorts E1 through E4 (NSCLC), and separately for Phase 2 Cohorts F1 and F2 (CRC).

At the first interim analysis (approximately 20 patients enrolled in each arm), a determination will be made whether any of the treatment arms may be dropped due to limited clinical activities. An integrated benefit-risk assessment from other data such as DOR, PK, target occupancy, tolerability, and safety will also be used to determine if a treatment arm should be stopped early due to futility. Otherwise, approximately 20 additional patients will be randomized or enrolled to each of the remaining treatment arms to confirm the efficacy signals. A final analysis of the Phase 2 ORR and PFS will be performed after all patients randomized to an arm have had the opportunity of having at least 3 months (for ORR evaluations) or 6 months (for PFS evaluations) of follow-up. See Section 9.5 for details of the interim analyses.

Enrollment may be discontinued due to futility if the response rate in the first 20 patients enrolled in any one arm is less than:

- 20% for arms E1, E2, or E3, and
- 10% for arms F1 or F2

In addition to ORR, an integrated benefit-risk assessment considering DOR, PK, target occupancy, tolerability, and safety will also be used to determine if a treatment arm should be stopped early due to futility.

9.4.3.2. Secondary Analyses

Assessments of PFS (CRC and Other Tumors cohorts) and OS (all cohorts) in Phase 2 will be performed as secondary analyses. Data from Phase 1 subjects will be summarized within each treatment cohort, but comparisons between cohorts will not be made. Data from Phase 2 subjects will be summarized within treatment arms. Comparisons between treatment arms will be made within tumor type. Survival rates at various time points (e.g., at 3, 6, 9, and 12 months), 75%, median, and 25% survival times will be reported, including differences between arms and their 95% confidence interval.

Progression-free survival is defined as the time from the date of randomization until the first occurrence of documented disease progression per RECIST v1.1 criteria, or death from any

cause in the absence of documented PD. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment. Progression-free survival will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. Progression-free survival curves, median PFS, and PFS rates at various time points with 95% confidence interval for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for PFS will be described in the SAP.

Symptomatic deterioration (i.e., symptomatic progression that is not confirmed per RECIST v1.1) will not be considered as tumor progression.

PFS Event/Censoring Scheme

Situation	**Event/Censor**	**Date of Event or Censor**
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate tumor assessment, per RECIST v1.1 criteria, or date of randomization (whichever is later)[a]
Unless		
No baseline radiologic tumor assessment available	Censored	Date of randomization
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals following randomization[a,b]	Censored	Date of randomization
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate tumor assessment or randomization (whichever is later)[a,b]	Censored	Date of last adequate tumor assessment, per RECIST v1.1 criteria, or date of randomization (whichever is later)[a]
New therapeutic anticancer treatment started prior to tumor progression or death	Censored	Date of last adequate radiological assessment prior to new therapeutic anticancer therapy[a]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SD = stable disease.

[a] Adequate tumor assessment per RECIST v1.1 criteria refers to an assessment with one of the following responses: CR, PR, SD, or PD.

[b] Refer to the statistical analysis plan for the definition of 2 scan intervals, including any adjustment for scan window.

9.4.4. Safety Analyses

All patients who receive at least 1 dose of any study therapy will be evaluated for safety and toxicity.

Safety analyses will include summaries of the following:

- DLTs at each DL
- AEs, including severity and possible relationship to study drug
- DLT-equivalent AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs and ECGs

9.4.5. PK/Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have sufficient samples collected to allow the estimation of LY3499446 PK parameters.

Pharmacokinetic parameter estimates for LY3499446 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be maximum concentration and area under the concentration-time curve ($AUC_{[0\text{-}tlast]}$, $AUC_{[0\text{-}\infty]}$) of LY3499446. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution, may be reported.

Additional analyses such as population PK analyses may also be conducted if deemed appropriate. Other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global PK management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Pharmacokinetic/pharmacodynamic analyses may be conducted to explore exposure-response relationships between LY3499446 concentrations in systemic circulation and various pharmacodynamic measures or clinical outcomes.

Plasma concentrations of erlotinib, abemaciclib and its metabolites, and serum concentrations of cetuximab at different time points will be summarized by descriptive statistics.

9.4.6. Other Analyses

9.4.6.1. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

9.4.6.2. Biomarker Analyses

Single-marker and/or multi-marker statistical analysis may be performed to explore the association between biomarkers, dose/exposure, and clinical outcomes.

9.5. Interim Analyses

In the Phase 1 portion of this study, data will be reviewed for safety on a cohort-by-cohort basis during the study, until the MTDs (or the highest DLs if MTDs are not reached) are determined for each treatment part. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each DL and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol. Before opening of the randomized Phase 2 portion of this study, a formal interim analysis including all Phase 1 data will be performed to conclude the safety profiles and RP2Ds.

The Phase 2 portion of Study JZKA comprises more than 3 cohorts and may warrant additional considerations to ensure patient safety.

Lilly has systematic and robust internal processes in place that ensure safety surveillance of development compounds in line with expectations of Regulatory Agencies. This includes processes with clearly described roles and responsibilities that are owned by Lilly's Global Patient Safety organization. These processes are designed to monitor the evolving safety profile (i.e., review of cumulative SAEs and other important safety information) by designated crossfunctional teams in a timely manner at predefined intervals or on an ad-hoc basis. In addition, a dedicated process may be used to perform unblinded comparisons of event rates for SAEs, as necessary.

This system ensures that the accumulating safety data derived from individual and multiple trials across a development program are reviewed on a regular basis and that important new safety information such as the need for protocol modification or other relevant safety-related material is identified and communicated to regulators and investigators appropriately and in a timely fashion. An internal review of aggregate safety data occurs on at least a quarterly basis or more frequently, as appropriate. Any serious adverse reactions (SARs) are reported within the required timeline for expedited reporting.

In addition to annual periodic safety updates and to further inform investigators, a line listing reports of SUSARs is created and distributed to investigators on a biannual (twice yearly) basis. Any significant potential risk/safety concerns that are being monitored, as well as any results being reported in other periodic reports for the compound, SAC decisions, and other significant

safety data (for example, nonclinical, clinical findings, and removal of SARs) are included in the report.

In the Phase 2 portion of this study, a safety review will be performed after the first 20 patients across all cohorts (NSCLC, CRC, and Other Tumors) are enrolled and treated for 1 cycle, and then every 6 months afterward.

In the Phase 2 portion of this study:

- For the NSCLC cohorts, an interim analysis of safety and efficacy is planned after approximately 20 patients in each cohort are treated and have completed 2 cycles or have discontinued before the first postbaseline tumor assessment. At this first interim analysis, the totality of data (including, but not limited to, safety and preliminary efficacy) will be used to determine if any of the treatment cohorts (E1, E2, E3) may be dropped due to limited clinical activities relative to the active comparator (E4). After the data cutoff date of this interim analysis, approximately 20 additional patients will be randomized to each of the remaining treatment arms to confirm the efficacy signals. Enrollment will be paused until the interim analysis has been completed.
- For the CRC cohorts, an interim analysis of safety and efficacy is planned after approximately 20 patients in each arm are treated and have completed 2 cycles or have discontinued before the first postbaseline tumor assessment. Enrollment will be paused until the interim analysis has been completed. Depending on the preliminary efficacy signal and totality of data, 1 arm may be dropped for futility. An additional 40 patients will be enrolled into the remaining arm. If no meaningful difference in efficacy or safety is observed in between the 2 arms, the 40 additional patients may be randomized at a 1:1 ratio, leading to approximately 80 total randomized patients (40 in each arm). Depending on the magnitude of clinical response observed in terms of durable objective responses, Study Protocol JZKA may be amended to provide for a more robust assessment of benefit/risk in this setting. The futility rules will be detailed in the SAP.
- For the Other Tumors cohort, an interim of safety and efficacy is planned after approximately 20 patients are treated and have completed 2 cycles or have discontinued before the first postbaseline tumor assessment. The trial will continue to enroll an additional 20 patients for the final analysis.

The interim analyses may be combined if they are expected to occur within a similar timeframe; interim analyses may also be combined with any prespecified safety review or annual reporting (such as an update to the IB or Development Safety Update Review, etc.).

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant and/or legal representative, when applicable, must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant and/or legal representative, when applicable, must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Lilly and international policies.

10.1.5. Data Quality Assurance

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data-capture system(s) will be stored by a third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system, and results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.7. Study and Site Closure

10.1.7.1. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.7.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed as indicated in the table below.
- If a local sample is required, it is important that the sample for central analysis is obtained at the same time (if applicable). If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (e.g., blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (e.g., hypertension, neutropenia, etc.), this should be entered into the CRF. Do not enter the test abnormality, enter the diagnosis or categorical term.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations, and any clinically significant abnormalities recorded in the AE eCRF.
- Investigators must document their review of each laboratory safety report. Enrollment and treatment decisions may be based upon local laboratory results. Discrepancies between local and central laboratory results will not be considered protocol deviations.

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Leukocytes (WBC)	**Serum Concentrations of:**
Neutrophils[c]	ALT
Lymphocytes	Albumin
Monocytes	Alkaline phosphatase
Eosinophils	AST
Basophils	Bilirubin, direct
Erythrocytes (RBC)	Bilirubin, total
HGB	BUN or blood urea
HCT	Calcium
PLT	Creatinine
	Creatine kinase
Urinalysis[b]	Glucose (random)
Blood	Magnesium
Glucose	Phosphorous
Ketones	Potassium
pH	Protein
Protein	Sodium
Specific gravity	
Urine leukocyte esterase[d]	**Pregnancy Test**[b,c]
	Urine or serum pregnancy test
Thyroid Function[b,e]	
TSH	**Coagulation**[b]
FT4	PT/INR
	aPTT

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRF = case report form; FT4 = free thyroxine; HCT = hematocrit; HGB = hemoglobin; INR = international normalized ratio; PLT = platelets; PT = prothrombin time; RBC = red blood cells; TSH = thyroid-stimulating hormone; WBC = white blood cells.

[a] Treatment and enrollment decisions will be based on local laboratory results.

Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[b] Local or investigator-designated laboratory.

[c] For female patients of childbearing potential.

[d] Urine microscopy may be used in place of the urine leukocyte esterase assessment to test for the presence of WBC.

[e] FT4 should only be collected if TSH is not within normal limits.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Women of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis and androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

    A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 follicle stimulating hormone measurement >40 mIU/mL is required.

    Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly Effective Methods[b] That Have Low User Dependency

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device
- Intrauterine hormone-releasing system[c]
- Bilateral tubal occlusion
- Vasectomized partner
- *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*

Highly Effective Methods[b] That Are User Dependent

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence

(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, or postovulation methods), withdrawal (coitus interruptus),

spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly CRP/CRS.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
HGB	
HCT	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
PLT	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
TBL	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Recommended Autoimmune Serology**
AST	Antinuclear antibody[a]
GGT	Antismooth muscle antibody[a]
CPK	Antiactin antibody[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CRF = case report form; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; HCT = hematocrit; HGB = hemoglobin; Ig = immunoglobulin; INR = international normalized ratio; PLT = platelets; RBC = red blood cells; TBL = total bilirubin; WBC = white blood cells.

[a] Assayed by local laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.5. Appendix 5: Country-Specific Requirements

10.5.1. Discontinuation of Inadvertently Enrolled Patients in the UK

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow-up should be performed as outlined in Section 1.3 (SoA), Section 8.3 (AEs and SAEs), and Section 8.2 (Safety Assessments) of the protocol.

10.6. Appendix 6: Inducers and Strong Inhibitors of CYP3A

The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St John's wort

Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl

Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

Abbreviation: CYP = cytochrome P450.

10.7. Appendix 7: Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance from **local laboratory results only.**

Cockcroft-Gault prediction of creatinine clearance from serum creatinine (Cockroft and Gault 1976)

For serum creatinine concentration in mg/dL:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(\textbf{140} - \textbf{age}^{a}) \times (\textbf{wt}) \times \textbf{0.85} \text{ (if female), or} \times \textbf{1.0} \text{ (if male)}}{\textbf{72} \times \textbf{serum creatinine} \text{ (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\textbf{CrCl} \text{ (mL/min)} = \frac{(\textbf{140} - \textbf{age}^{a}) \times (\textbf{wt}) \times \textbf{0.85} \text{ (if female), or} \times \textbf{1.0} \text{ (if male)}}{\textbf{0.81} \times \textbf{serum creatinine} \text{ (μmol/L)}}$$

Abbreviations: CrCl = creatinine clearance; wt = weight.

[a] Age in years, wt in kilograms.

Source: Cockcroft and Gault 1976.

10.8. Appendix 8: Dose-Finding Algorithm of the mTPI-2 Method Showing Number of Patients Treated

Number of Patients

Number of Patients with DLTs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	D	D	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		DU *	D	D	D	D	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			DU	DU	D	D	D	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E
4				DU	DU	DU	D	D	D	D	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E
5					DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	E	E	E	E	E	E	E
6						DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	S	S	S	S	E	E	E
7							DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	D	S	S	S	S
8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	D	S
9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17																	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU	DU	DU	DU	DU
19																			DU	DU	DU	DU	DU	DU	DU
20																				DU	DU	DU	DU	DU	DU
21																					DU	DU	DU	DU	DU
22																						DU	DU	DU	DU
23																							DU	DU	DU
24																								DU	DU
25																									DU

n = 25, p_T = 0.30, ε_1 = 0.03, ε_2 = 0.03

E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial;

* If at the first dose level, users can choose to early-terminate the trial or not based on their own discretion.

Abbreviations: DLT = dose-limiting toxicity; mTPI-2 = modified toxicity probability interval-2.

The number of patients dosed at a given DL is shown in the columns (X-axis), while the number of DLTs experienced is shown in the rows (Y-axis). The rules in this figure will be used for each DL evaluated; the patient numbers and DLTs do not carry over from cohort to cohort. By locating the intersection of the number of patients dosed and the number of DLTs, 1 of 4 predefined rules is used:

- E: Escalate the dose
- S: Stay at the same dose
- D: De-escalate the dose
- DU: De-escalate the dose due to unacceptable toxicity. The dose cannot be re-escalated to this DL at a future point in the escalation.

For example, within a cohort:

- If 1 of 3 patients experiences a DLT, stay at the same dose (see "S" in column 3, row 1). The fourth patient must be treated at the same DL.

- If 1 of 6 patients experiences a DLT, escalate the dose (see “E” at column 6, row 1).
- If 2 of 3 patients experience a DLT the dose to treat the next patient is de-escalated (see “D” at column 3, row 2). If 5 of 7 patients experience a DLT, the dose is determined to be unacceptably toxic and will never be used again in the trial (see “DU” at column 7, row 5).

10.9. Appendix 9: Examples of Sensitive and Moderately Sensitive CYP2C9 and CYP2C19 Substrates

The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Isoform	Sensitive substrates	Moderately sensitive substrates
CYP2C9	celecoxib	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole, rabeprazole, voriconazole

Abbreviation: CYP = cytochrome P450.

10.10. Appendix 10: Abbreviations

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BOR	best overall response
CDK	cyclin-dependent kinase
CFR	Code of Federal Regulations
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRP/CRS	clinical research physician/clinical research scientist: Individual responsible for the medical conduct of the study. Responsibilities of the CRP/CRS may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450

CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DL	dose level
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GDP	guanosine diphosphate
GEF	guanine nucleotide exchange factors
GFR	glomerular filtration rate
GTP	guanosine triphosphate
HNSTD	highest nonseverely toxic dose
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
ILD	interstitial lung disease

Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MATE	multidrug and toxin extrusion protein
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI-2	modified toxicity probability interval-2
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	orally
PR	partial response
QD	daily

QOD	once every other day
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of activities
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
UK	United Kingdom
ULN	upper limit of normal
UN	unknown
WOCBP	women of childbearing potential

10.11. Appendix 11: Protocol Amendment History

Amendment (a)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment incorporates changes according to regulatory agency feedback. Additionally, clarifications were made throughout the document to improve consistency and readability for sites and investigators.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis; Section 4.1.1.1 Dose Escalation Method; Section 9.5: Interim Analyses	Additional language added to clarify enrollment	Per regulatory feedback
Section 1.2.1: Phase 1 Schema; Section 1.2.2: Phase 2 Schema	Moved start of enrollment of erlotinib cohorts to match timing of abemaciclib cohorts in Phase 1	Per regulatory feedback
Section 1.3: Schedule of Activities	Added footnotes specifying duration of short-term and long-term follow-up	Per regulatory feedback
Section 2.3: Benefit/Risk Assessment	Provided additional information for erlotinib, cetuximab, and abemaciclib combinations	Per regulatory feedback
Section 3: Objectives and Endpoints; Section 1.1 Synopsis	Added separate secondary objective bullet for Other tumors cohort	Per regulatory feedback
Section 4.1.1.1: Dose Escalation method	Added conditional statement for starting LY3499446 dose at [redacted]	Per regulatory feedback
Section 4.1.1.1: Dose Escalation Method; Section 9.1: Statistical Hypotheses; Appendix 8	Changed equivalence interval to (27%, 33%); updated dose-finding algorithm figure	Per regulatory feedback
Section 4.1.1.2: Dose-Limiting Toxicity Determination	Revised DLT criteria	Per regulatory feedback
Section 5.1: Inclusion Criteria; Section 5.2: Exclusion Criteria	Modified inclusion/exclusion criteria 2, 16, and 19; Added exclusion 27.	Per regulatory feedback
Section 6.1: Study Intervention(s)	Added dosing language relative to	Per regulatory feedback

Section # and Name	Description of Change	Brief Rationale
Administered	food intake	
Section 6.3: Measures to Minimize Bias: Randomization and Blinding	Revised stratification factors	Per regulatory feedback
Section 6.5: Concomitant Therapy; Section 6.5.1: Use of Gastric pH Modifying Agents	Provided additional cautionary language for erlotinib	Per regulatory feedback
Section 6.5.3: Supportive Management for Diarrhea	Modified diarrhea management language to be applicable for all study drugs	Per regulatory feedback
Section 6.6.1: Dose Modification of LY3499446	Modified diarrhea dose modifications and added guidance for interstitial lung disease	Per regulatory feedback
Section 6.6.6 Dose Modification for Grade 3 Toxicities Not Clearly Related to LY3499446 or Drug Given in Combination	Guidance added for Grade 3 toxicities not related to LY3499446 or combination drugs	Per regulatory feedback
Section 9.2: Sample Size Determination; 9.4.3.1: Primary Analyses	Additional statistical justification provided and clarity added to descriptions of Phase 2 cohorts	Per regulatory feedback
Section 1.3: Schedule of Activities	Moved Phase 2 CRC biomarker serum samples on C2D1 and C3D1 to C1D8 and C1D15	Modified to align samples with biopsy time points
Section 1.3: Schedule of Activities	Removed docetaxel line from Phase 1a section	Docetaxel will not be administered in Phase 1a
Section 9.3: Populations for Analyses	Clarified that 2 of 3 cetuximab doses are required for cetuximab combination cohorts	Modified for consistency with DLT evaluability
Throughout	Minor editorial and formatting changes	Minor, therefore not summarized

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